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ORIGINAL ARTICLES

A FATAL ANAPHYLACTIC REACTION TO ORAL PENICILLIN

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NUMEROUS instances of anaphylactic reactions following the parenteral administration of penicillin have been recorded in the literature. However, there have been comparatively few such cases reported from oral penicillin therapy. Only two of the patients died. To our knowledge the following case report represents the thirtieth described case of anaphylaxis from oral penicillin and the third fatality. It includes a complete postmortem examination and an interesting family history.

In 1953, Pierce[1] reported the first anaphylactic reaction following oral penicillin therapy. About the same time, Mayer and his associates[2] reported six anaphylactic reactions from parenteral penicillin administration, and noted that the one fatal reaction had been preceded by a fainting episode upon the use of a penicillin troche. Welch and associates[3] conducted a survey of severe antibiotic reactions and learned of one fatal reaction to oral penicillin. This case has been summarized in an article by Weiner and colleagues,[4] who listed the autopsy diagnoses of mild pulmonary edema, cardiac dilatation, and anaphylaxis. Weiner and his group added a nonfatal anaphylactic reaction of their own, and summarized another case reported to them by Feinberg. Case reports of twenty additional nonfatal shock-like reactions to oral penicillin,[5-18] and three from penicillin lozenges[19-21] have been published. The second fatal shock reaction from oral penicillin therapy was reported in 1957 by Mason.[22] Autopsy examination was not permitted in Mason's patient. Welch and co-workers[3] and Burdick[23] have alluded to other similar nonfatal reactions and, in a recent nation-wide survey, Welch[24] counted forty-nine anaphylactic reactions from oral penicillin preparations out of a total of 793 such reactions from all forms of penicillin. However, no specific case information was recorded.

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CASE REPORT

M. P., a 21-year-old Negro man—an animal caretaker, complained of headache on Aug. 14, 1957, and took aspirin. He had headache the next day and complained of "catching a cold." Immediately after supper, on his own initiative, he took one oral dose of penicillin powder (1,000,000 units of penicillin G sodium) in water. Immediately afterward he developed a hacking cough, with a strangling or choking sensation. Within a minute he fell back, bumped his head on the floor, jerked his head three times, then got up on his feet only to slouch down again. He was coughing at this time. A swelling of the nose and mouth, with mucoid nasal discharge, was noted. The patient's father, who related this history, helped him up, but the patient became limp. The father removed the patient's dentures and found the pulse to be present, but observed no coughing, dyspnea, or sweating. The patient seemed unconscious. He became incontinent and developed an ashen color with circumoral pallor. En route to the hospital the face twitched to the left side and the head jerked to one side. At the hospital more twitching was noted and the patient was limp. No pulse was present. The patient was pronounced dead approximately twenty to thirty minutes following the onset of symptoms.

Prior to this illness the patient had been considered in good health. He was a nervous person, easily excited and upset and, at times, somewhat depressed. In the year before his death he had gained thirty pounds, and weighed approximately 200 pounds. There was some increase in sweating in his last week of life, although he had always noted excessive sweating. He had complained of frequent headaches since a dental extraction in March, 1957. He experienced much sneezing every morning, without other nasal symptoms.

In 1954, at age 18, the patient had been given intramuscular penicillin for an infected knee. In 1956, he had received prophylactic penicillin therapy intramuscularly when a sister was found to have rheumatic fever. In November, 1956, he was first given the penicillin powder by mouth because of a cold, but he took only one dose. No known untoward effects resulted. Tonsillectomy had been performed at the age of 12.

The patient was one of thirteen children, of whom eight survived. He was unmarried. His mother and father were living and well, but the mother had had rheumatic fever. Three of the surviving sisters had had rheumatic fever, and one of these had "bronchial trouble." Another sister had hay fever. One brother had a history of rheumatic fever and of eczema caused by milk. Another brother had hay fever and asthma, and was rejected for military service because of a "bad heart." This brother is presently confined to a mental hospital for a nervous condition.

Four sisters were dead: two died in infancy, one committed suicide at age 22, and the fourth died at age 26, allegedly from tetracycline toxicity during treatment of actinomycosis of an upper extremity. The latter sister had a history of rheumatic fever and of hives from penicillin.

Autopsy Findings.—At postmortem examination, the body was that of a well-developed 21-year-old Negro male, weighing an estimated 210 pounds and measuring 165 cm. in length. Both lungs were voluminous and together weighed 810 grams. They were soft and pillowy throughout. The posterior portions were somewhat heavy. Microscopic examination showed moderate emphysema and chronic passive congestion with "heart failure" cells in the alveoli. The heart weighed 400 grams. The left ventricle measured 1.8 cm. in thickness and the right ventricle measured 0.4 cm. in thickness. The valves appeared competent. The thymus weighed 30 grams, but was grossly and microscopically normal. The brain weighed 1,300 grams. There was an excessive amount of fluid in the subarachnoid space. The cerebellar tonsils showed moderate pressure coning. The microscopic examination of the brain revealed moderate generalized edema. There was no evidence of brain injury. The remaining organs showed no significant changes, either grossly or microscopically. It was noted that blood collected from the right heart at the time of autopsy failed to clot after 72 hours while remaining under refrigeration. Bacteriologic examinations were negative.

DISCUSSION

What was the cause of death in this patient? The history of penicillin ingestion, the immediate reaction and subsequent course, and the autopsy findings are consistent with the diagnosis of anaphylaxis due to penicillin hypersensitivity. Other causes of sudden death, such as coronary occlusion, cerebral vascular accident, embolism, hemorrhage, laryngeal edema, and tracheal obstruction were not found at postmortem examination. There was no apparent reason to consider other drug reactions or cardiac arrhythmias. Unfortunately, the blood specimen obtained at postmortem examination was inadvertently discarded before any tests for penicillin antibodies could be made.

How did sensitization occur? The history of previous penicillin administration by intramuscular and oral routes would indicate that ample opportunity for sensitization had occurred. Twenty-six of the twenty-nine patients reported with anaphylactic reactions to oral penicillin had previously received penicillin intramuscularly. In one case,[22] penicillin had been given previously only by mouth. In one case,[20] no previous penicillin therapy was recalled, and, in one case,[4] this information was not recorded. This would suggest that anaphylactic sensitization to penicillin occurs mainly by the parenteral route and rarely by the oral route.

Why did the reaction occur so rapidly? Obviously, the penicillin was absorbed rapidly, and in sufficient quantity to react with antibody and cause anaphylaxis. Penicillin is known to be absorbed sublingually[25] and by way of mucous membranes, as well as via the intestinal tract. Once antibodies are present, elicitation of symptoms can occur following contact with antigen administered by any route—parenteral, oral, or topical.

What was the role of heredity? This patient had one parent and five siblings with histories of rheumatic fever, and he had four siblings with allergic diseases of the "atopic" group. This family history is striking. It has been reported that penicillin anaphylaxis is more likely to occur in patients with other allergic disorders.[26] The role of other factors, such as constitutional, psychogenic, or neurologic factors is only speculative, but should be considered.

This case report again calls attention to the importance of the indiscriminate use of penicillin and the dangers of self-medication. In instances where penicillin is indicated, oral administration, where applicable and effective, would be the preferred route in order to minimize the risk of sensitization. When a patient has had previous penicillin therapy, careful inquiry into the history for any untoward reaction is essential in order to anticipate and avoid possible sensitivity reactions. Of the twenty-nine collected cases of anaphylaxis from oral penicillin, in ten of them there had been previous reactions, either local or systemic. Any patient with a history of such a reaction should not receive penicillin by any route, except under circumstances which justify the risk of an untoward reaction.

Skin testing with penicillin prior to its administration has been advocated by many authors in order to identify possible anaphylactic sensitization in those

patients previously treated with penicillin without untoward reaction.[27-30] Such tests have been said by some authors to be unreliable,[31] impractical, and, even, dangerous. However, these objections are based largely on the results of testing patients after the occurrence of penicillin reactions, in whom variable percentages exhibit positive skin tests or eye tests.[30, 32] Testing patients with known reactions is certainly dangerous and should not be done as a general rule. Indeed, of the twenty-nine recorded cases of anaphylaxis from oral penicillin therapy, nine patients were subsequently skin-tested with penicillin and seven again developed constitutional symptoms. The use of skin and eye tests prior to administration of penicillin was described by Smith,[33] who found such testing to be simple and accurate in identifying patients susceptible to penicillin anaphylaxis. Because of the small percentage of anaphylactic reactions that would be expected in one individual's experience, many similar studies will be necessary to permit statistical evaluation of these procedures. On the basis of present information, we would agree that proper testing appears to be safer than the administration of a full therapeutic dose of penicillin without testing, and offers the possibility of minimizing the occurrence of serious or fatal immediate anaphylactic reactions. We would advise routine testing in all patients previously treated with penicillin without known allergic reaction. The most practical technique might be the scratch test using the full strength or dilutions of penicillin, depending on the individual situation. In those exhibiting positive reactions, penicillin should not be administered unless the risk of the disease is as great as the risk of an untoward reaction.

SUMMARY

A case of fatal anaphylaxis following oral administration of penicillin is reported. Autopsy data are included. The importance of the indiscriminate use of penicillin and the danger of self-medication are emphasized. Methods for the prevention of anaphylactic reactions are discussed.

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FORMATION AND DESTRUCTION OF C^{14} HISTAMINE IN HUMAN LUNG TISSUE IN VITRO

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SCHILD, Hawkins, Mongar, and Herxheimer[1] presented strong evidence that histamine plays a role in the reaction of bronchial muscle of asthmatic subjects to allergens. It is not known how the histamine that is released in this reaction is formed, nor is it known what means the human lung tissue has to inactivate histamine.

In the present in vitro experiments we have studied the formation and catabolism of histamine in lung tissue from nonasthmatic subjects.

MATERIAL AND METHODS

The lung tissue was obtained from surgical operations for lung diseases. It was macroscopically normal. The incubations took place within two hours after the tissue had been excised. All instruments and glass used for the incubations had been sterilized.

Formation of Histamine From C^{14}-Labelled L-*Histidine.*—The tissue was minced with scissors and aliquots weighing 2 to 3 grams were put in beakers. Samples heated to 100° C. were used as blanks. The volume of the sample was made up to 5 ml. with 0.1 M phosphate buffer (pH 7.4) containing aminoguanidine (a histaminase inhibitor) in a concentration of 10^{-4} M and C^{14}-labelled L-histidine (obtained from the Radiochemical Centre, Amersham, England) added to give a concentration of 8 to 40 μg per milliliter of the sample.

The incubations took place in a shaking incubator at 37° C. in an atmosphere of nitrogen. After three hours, nonradioactive histamine (40 mg. base) was added to serve as carrier in the extraction and purification of the C^{14} histamine which followed the scheme described by Schayer[2] and Kahlson, Rosengren, Westling, and White.[3]

Metabolism of C^{14}-Labelled Histamine.—Two to three gram aliquots of minced lung tissue were incubated with C^{14}-labelled histamine (about 0.4 μg/ml. of sample), the total volume of the sample being made up to 5 ml. with phosphate buffer. The gas phase in the incubation was air, otherwise the conditions were the same as used to demonstrate formation of histamine.

After three hours, the sample was diluted to 30 ml. with 0.1 N HCl and homogenized. Aliquots were taken and analyzed for their content of C^{14}-labelled histamine, 1-methyl-4-(β-aminoethyl) imidazole (methylhistamine), 1-methylimidazole-4-acetic acid (methylimidazole-acetic acid) or imidazole acetic acid (free or conjugated) with Schayer's isotope dilution technique, as used by Lindell and Schayer.[4]

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The ways of assessing the radioactivity of the compounds extracted and purified from the samples have been described.[3, 4]

One microgram of the C^{14}-labelled histamine formed from the labelled L-histidine used here, gives 3,000 counts per minute (c. p. m.) when assayed under our standardized conditions. One microgram of the C^{14} histamine used for study of the metabolism of histamine in lung tissue gives 2,040 c. p. m. under the same conditions.

Test for the Growth of Bacteria in the Samples.—At the end of the incubations a small amount of the sample was transferred to a test tube containing a nutrient broth. The tube was placed at 37° C. for 48 hours and then examined for bacterial growth.[5]

RESULTS

Histamine Formation in Lung Tissue.—Table I shows the results of an incubation of tissue from one human lung with C^{14}-labelled L-histidine. It may be seen that the results of duplicate samples agreed well. The samples had reached constant radioactivity after the second recrystallizations of the histamine in the form of the *p*-iodophenylsulphonyl derivative. The differences between samples and blanks were about 30 c. p. m., corresponding to 10 nanograms C^{14} histamine base. Penicillin and streptomycin in the amounts used did not interfere with the histamine formation. Penicillin and streptomycin in these concentrations are used to prevent bacterial growth in tissue cultures.[6]

TABLE I. FORMATION OF C^{14} HISTAMINE FROM C^{14}-LABELLED L-HISTIDINE IN 7 ALIQUOTS OF MINCED TISSUE FROM A HUMAN LUNG IN VITRO*

					STREPTOMYCIN (100 μG/ML.) PENICILLIN (60 U./ML.)		
	A†	B†	C	D	E†	F	G
Radioactivity of pipsyl-histamine prepared from sample after							
2nd recrystallization	64	73	97	100	74	114	104
3rd recrystallization	63	75	96	96	72	102	105

*Each sample contained 3 grams of lung, 66 μg C^{14} histidine, and phosphate buffer (pH 7.4) with aminoguanidine in a concentration of 10^{-4}M. Total volume of each sample was 5 ml.

†Samples A, B, and E are heat-inactivated blanks. The figures refer to counts per minute above background.

Our test for bacterial growth in these samples was negative.

Table II shows the results of an experiment in which the concentration of C^{14} histidine was varied.

TABLE II. THE EFFECT OF CHANGE IN SUBSTRATE CONCENTRATION ON THE HISTAMINE FORMATION IN HUMAN LUNG TISSUE*

	A†	B†	C	D	E†	F	G
Initial concentration of C^{14} histidine (μg/ml.)	8	8	8	8	40	40	40
Amount of C^{14} histamine formed in 3 hours (nanograms)	3	3	6	8	16	35	43

*Each sample contained 2 grams of minced lung. Conditions otherwise as in the experiment of Table I.

†A, B, and E are heat-inactivated blanks.

In samples as well as in blanks, the C^{14} histamine that was formed increased with increase in histidine concentration. The net value for histamine formation (sample minus blank) increased about five times with a fivefold increase in the substrate concentration; about 0.1 per cent of the C^{14} histidine was recovered as C^{14} histamine.

Table III shows the amount of C^{14} histamine formed per gram of lung in the experiments of the present investigation. The table also contains some data about the subjects from whom the lung tissue was obtained.

TABLE III. HISTAMINE FORMATION OF LUNG TISSUE FROM SIX PATIENTS (BLANKS HAVE BEEN SUBTRACTED)

	PATIENT					
	1	2	3	4	5	6
Age	60	72	44	71	51	66
Sex	female	female	male	male	male	male
Antibiotics given preoperatively	strepto-mycin	—	strepto-mycin	strepto-mycin	—	—
Pulmonary disease	bronchi-ectasies	cancer	tuberculosis	cancer	cancer	cancer
Amount of C^{14} histamine formed per gram of lung (nanograms)	5	2	4	15	4	3

Thus, incubation of lung tissue from these six patients, with C^{14}-labelled L-histidine led to the formation of small amounts of C^{14} histamine. The histamine was found in samples which contained penicillin and streptomycin and from which bacteria could not be grown. This is considered evidence that the histamine formation was due to an agent in the lung tissue, probably an enzyme (histidine decarboxylase) which was inactivated by heating the sample to 100° C.

Metabolism of C^{14}-Labelled Histamine in Lung Tissue.—What means does the human lung tissue possess to inactivate histamine? In perfusion experiments in cats where fairly large quantities of histamine were used, evidence has been obtained that the lungs can take up histamine and store it in unchanged form.[7] However, more recent experiments with injections of smaller, more "physiological," quantities of histamine do not support the view that histamine can be taken up and stored for any longer period of time in any human tissue.[8, 9] It seems more likely that inactivation of histamine in the lungs would involve an enzymic destruction of the amine. According to Karady, Rose, and Brown,[10] the lungs of the rat contain histaminase. Zeller, Birkhäuser, Mislin, and Wenk[11] found evidence of histaminase activity in human lung tissue.

In experiments with heart lung preparations from cats, evidence was obtained that the most important means of inactivation of histamine was the histamine-methylating enzyme.[12]

The following experiment was carried out in order to obtain more information about the capacity of human lung tissue to metabolize histamine–lung tissue from Subject 4 was minced and incubated with histamine labelled with C^{14}. The experimental conditions and the results are given in Table IV.

TABLE IV. METABOLISM OF C^{14} HISTAMINE IN HUMAN LUNG TISSUE IN VITRO*

	A	B AMINOGUANIDINE 10^{-4} M
Unchanged histamine	2,100	1,700
Methylhistamine	1,300	1,300
Methylimidazole acetic acid	300	400
Imidazole acetic acid (free and conjugated)	200	200
Total amount of radioactivity recovered	3,900	3,600

Each sample contained 2 grams of minced lung and 2 μg C^{14} histamine (giving 4,080 c. p. m. under our standardized conditions of assay); total volume of sample made up to 5 ml. with 0.1 M phosphate buffer. Incubation at 37° C. for 3 hours in an atmosphere of air.
All values are given in counts per minute above background.

It may be seen that methylhistamine was by far the most important metabolite of histamine. An experiment with lung tissue from another subject gave similar results. Judging from these experiments, less than 25 per cent of the methylhistamine formed was further oxidized to methylimidazole acetic acid. Only 5 per cent of the C^{14} histamine added to the samples was oxidized to imidazole acetic acid (free or conjugated). Since this oxidation was not influenced by aminoguanidine, a strong inhibitor of histaminase, it may have been due to amine oxidase.[13]

Since human lung tissue can methylate histamine fairly rapidly in vitro it seemed possible that, in the experiments where histamine formation from labelled histidine was studied, a large proportion of the histamine formed was metabolized to methylhistamine and thus escaped detection.

For this reason the experiment described in Table V was performed.

TABLE V. FORMATION OF C^{14}-LABELLED METHYLHISTAMINE AND HISTAMINE IN LUNG TISSUE INCUBATED WITH C^{14} HISTIDINE*

	A†	B†		C†	D†
C^{14} histamine formed (nanograms)	25	30	C^{14} methylhistamine formed	1	<1

*Each sample contained 2 grams of minced lung in phosphate buffer with 9 μg C^{14} histidine per milliliter. Total volume of sample 10 ml. Conditions otherwise as described in Table I.
†Samples A and B were assayed for histamine and samples C and D for methylhistamine.

There was hardly any measurable amount of C^{14} methylhistamine in these samples. (We have assayed these samples only for methylhistamine. To our knowledge there is at the present time no reliable method for assay of the other known histamine metabolites in samples containing C^{14} histidine and histidine metabolites.)

The results of this experiment suggest that the histamine formed in human lung tissue is inaccessible to the histamine-methylating enzyme also present in the lung tissue, possibly because the newly formed histamine is bound in the (mast?) cells. If this is so, the histamine formation and mode of binding in human lung tissue are similar to that in rat skin in vitro (Schayer, Davis, and Smiley[14]), but differ from that in the liver of the rat fetus (Kahlson, Rosengren, and White[15]).

The rate of histamine formation in lung tissue from nonasthmatic subjects observed in these experiments may seem small—2 to 15 nanogram histamine

base per gram tissue in incubations lasting three hours (about 0.1 per cent of the C^{14} histidine being converted to histamine). This rate of histamine formation is, however, of the same order of magnitude as that in the skin of normal rats (Schayer and co-workers[14]).

In view of Schayer's[16] discovery that the histidine decarboxylase activity of rat skin increases after liberation of histamine with Compound 48/80, it would be of great interest to study the histamine formation in lung tissue from asthmatic subjects.

SUMMARY

When C^{14}-labelled L-histidine was incubated with human lung tissue, C^{14} histamine was formed.

C^{14}-labelled histamine incubated with human lung tissue was metabolized, the major metabolite being methylhistamine (1-methyl-4-[β-aminoethyl] imidazole).

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CENTRAL NERVOUS ACTIVITY IN GUINEA PIG ANAPHYLAXIS

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IN RECENT years there has been a renewal of interest in the relation of the central nervous system to anaphylaxis. Szentivanyi and his associates[1, 2, 3] reported that bilateral focal lesions of the tuberal region of the hypothalamus produced inhibition of generalized anaphylaxis, local anaphylaxis (Schultz-Dale test), and antibody production in both rabbits and guinea pigs. Freedman and Fenichel[4] reported inhibition of anaphylaxis in the guinea pig with bilaterally symmetrical lesions of the midbrain reticulum at the level of the superior colliculus.

Observation of electrical activity in the central nervous system during anaphylaxis has been limited to studies of surface recordings by Gozzano and Colombati,[5] and by Brandon.[6] The former reported cortical bursts of high potential spikes, "similar to those seen in epilepsy," during generalized anaphylactic shock in rabbits immunized to horse serum and challenged by the intravenous route. They also reported similar activity limited to the local site of application when challenge was by topical application of horse serum to the exposed brain. Brandon[6] observed a variety of electrical phenomena recorded over the cortex and spinal cord of guinea pigs sensitized to horse serum and challenged by either the intravenous or intraperitoneal routes. In the former, he observed high potential spikes followed by depression of activity and exitus, while in the latter the spike activity was followed by periods of slow wave desynchronization intermixed with periods of generalized depression of electrical activity.

As there have been no reports of the electrical activity of subcortical centers to our knowledge, the present study was undertaken to determine if specific electrical phenomena in the brain areas implicated by the extirpation studies cited above could be observed in anaphylaxis.

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MATERIAL AND METHODS

Thirty-five young adult albino guinea pigs of both sexes and of an inbred strain,* weighing 500 to 700 grams, were used in these experiments. Eight were passively immunized by the intravenous injection of 0.1 ml. per 100 grams of body weight of a high titer (approximately 4 mg. precipitin Ab protein/c.c.) rabbit anti-BSA (bovine serum albumin) serum. They were challenged twenty-four hours after sensitization by either the intravenous injection of 5 mg. of bovine serum albumin in a 1 per cent aqueous solution or by the intraperitoneal injection of 250 mg. of bovine serum albumin in a 10 per cent aqueous solution.

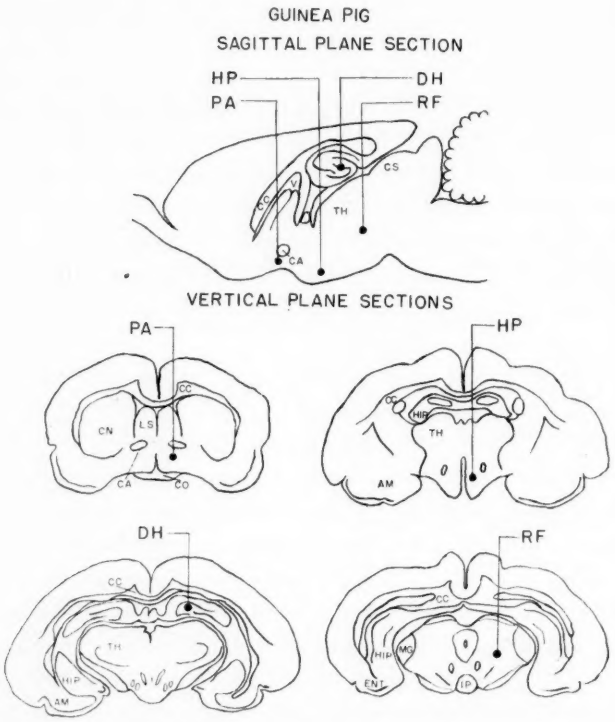

Fig. 1.—Diagrammatic representation of electrode placements in the guinea pig brain. *HP* = Hypothalamus. *DH* = Dorsal hippocampus. *RF* = Reticular formation. *PA* = Preoptic area. *CN* = Caudate nucleus. *CA* = Anterior commissure. *CO* = Optic chiasma. *TH* = Thalamus. *HIP* = Hippocampus. *AM* = Amygdala. *LS* = Lateral septal nuclei. *ENT* = Entorhinal area. *MG* = Medial geniculate. *IP* = Interpeduncular nucleus.

Twenty-three animals were actively immunized by the subcutaneous injection of 2.5 mg. of crystalline egg albumin in 0.5 c.c. of physiologic saline emulsified with 0.5 c.c. of Arlacel-Baylol mixture, after the manner of Freund.[7] These animals were challenged three weeks after immunization, six by the intraperitoneal injection of 500 mg. of egg albumin in a 25 per cent aqueous solution, thirteen by the intravenous injection of 2.5 mg. of egg albumin in a 1 per cent aqueous solution. In this group of animals it was found expedient to give, as a

*Kindly furnished by Dr. Dan H. Campbell, California Institute of Technology, Pasadena, Calif.

"supportive" measure, 2 mg. of Benadryl intravenously fifteen minutes prior to challenge. This dose does not inhibit the development of anaphylaxis, but obviates early death and prolongs the shock state.

Two normal animals were given intravenous injections of histamine phosphate (250 μg histamine base/c.c.) at a dose of 50 μg per kilogram of body weight.

Two normal animals were subjected to asphyxia by suspension of artificial respiration.

Light ether anesthesia was used during tracheal cannulation and exposure of the brain. Operative sites and pressure points were infiltrated with 1 per cent procaine hydrochloride. Immobilization was secured with a single intraperitoneal injection of D-tubocurarine at a dose of 0.4 mg. per kilogram. Artificial respiration was carried on throughout the remainder of the experiment.

Prior to the investigation, a stereotaxic atlas of the guinea pig brain was prepared by one of us (C. W. D.). Using a slightly modified Johnson stereotaxic instrument, precise localization of concentric 1 mm. diameter steel electrodes in the brain was obtained. Bipolar records of central nervous activity were recorded, using a Grass Model IV electroencephalographic instrument. At the conclusion of all experiments, the brain was removed and precise disposition of the electrode tracks subsequently determined from serial Nissl sections, cut frozen at a thickness of 50 microns.

The regions studied included the cerebral cortex, hypothalamus, preoptic area, dorsal hippocampus, and reticular formation (Fig. 1). A unipolar electrocardiogram (ECG) was recorded concomitantly.

RESULTS

Benadryl caused a transient increase in the excitability of all centers studied without significant change in the ECG. Within a maximum of ten minutes, the electroencephalogram (EEG) returned to normal and nervous activity resembled that observed in the control records.

In all animals tested, a marked biological variation in the nervous response during anaphylaxis was observed. The most common finding after intravenous injection of antigen was the development, within three to six minutes, of high amplitude spike activity in the dorsal hippocampus and in the preoptic and hypothalamic areas, with a concomitant flattening of the background activity in all regions, especially in the dorsal hippocampus (Fig. 2, *B*). For the next five to ten minutes the background activity became further depressed and the incidence of spiking more random (Fig. 2, *C*). No significant ECG changes were observed during this time. After this period, a gradual return of nervous activity was recorded, but recovery was never complete (Fig. 2, *D*). It was at this time that ECG changes became pronounced, beginning at first with flattening of the T wave and changes in the S-T segment. These changes were followed by prolongation of the P-R interval, progressed into various types of heart block and conduction defects, and finally to complete disorganization of the ECG pattern. As the ECG pattern became more chaotic, spiking was again

seen in the dorsal hippocampus (Fig. 2, *E*), and to a lesser extent in the reticular formation. Quite often spiking was also observed in the hypothalamic, preoptic, and cerebral cortical regions. In some experiments, the EEG and ECG changes described above would be repeated, and if Adrenalin (0.05 c.c. of a 1:1,000 solution) was administered intravenously before irreversible cardiac deterioration, a normal ECG would result and at the same time nervous activity would assume a near normal pattern.

A few animals were quite resistant to anaphylaxis (Fig. 3). In these it was observed that the dorsal hippocampus appeared to be the most affected structure. Long trains of regular 4 to 6/second waves, often observed in the hippocampus under normal conditions, were replaced after fifteen to twenty minutes after intravenous challenge by much shorter trains of regular waves interspersed with desynchronized activity (Fig. 3, *B*). At this time the ECG showed early changes. This state of nervous activity was maintained for very long periods without any deterioration in the ECG. If a second injection of antigen was administered thirty to forty minutes after the initial challenge, the dorsal hippocampus activity became irregular and further changes in the ECG became evident shortly thereafter (Fig. 3, *C*). As the ECG became more and more markedly abnormal, the nervous activity became depressed with simultaneous spiking in the cerebral cortex, hypothalamus, and dorsal hippocampus (Fig. 3, *D* and *E*). As in all other experiments, the dorsal hippocampus was the first to become depressed.

Other signs of abnormal nervous activity observed in anaphylaxis were the appearance of high amplitude slow waves broken at random by spike formations in the cerebral cortex, dorsal hippocampus, and hypothalamic and preoptic areas. During the depressed state, regular 4/second slow waves were often observed in the dorsal hippocampus. These waves gradually lost amplitude as the period of complete depression of nervous activity approached. Throughout these studies, the reticular formation appeared to be the least affected of the regions studied.

The EEG and ECG effects noted above in actively sensitized animals during anaphylaxis were also observed in those passively sensitized.

The same sequence of events was observed when the intraperitoneal route was employed for challenge injections in either actively or passively sensitized animals. However, after intraperitoneal injection, anaphylactic signs did not develop for from forty to eighty minutes and the EEG and ECG effects described above were distributed over a much longer period. Due to the irregularity and delay in time of onset of anaphylaxis, this route was abandoned in favor of the intravenous route plus Benadryl support as the most expedient method of experimentation.

Since it is well established that histamine release plays a large role in the production of anaphylactic symptoms in the guinea pig and that many, if not all, of the symptoms and signs of anaphylaxis can be produced in this species by injection of histamine, the EEG and ECG effects of intravenous histamine were recorded in normal guinea pigs as additional observations. In both instances, three to five seconds after injection, marked ECG changes were observed (Fig. 4, *B*), although very little modification in nervous activity was observed

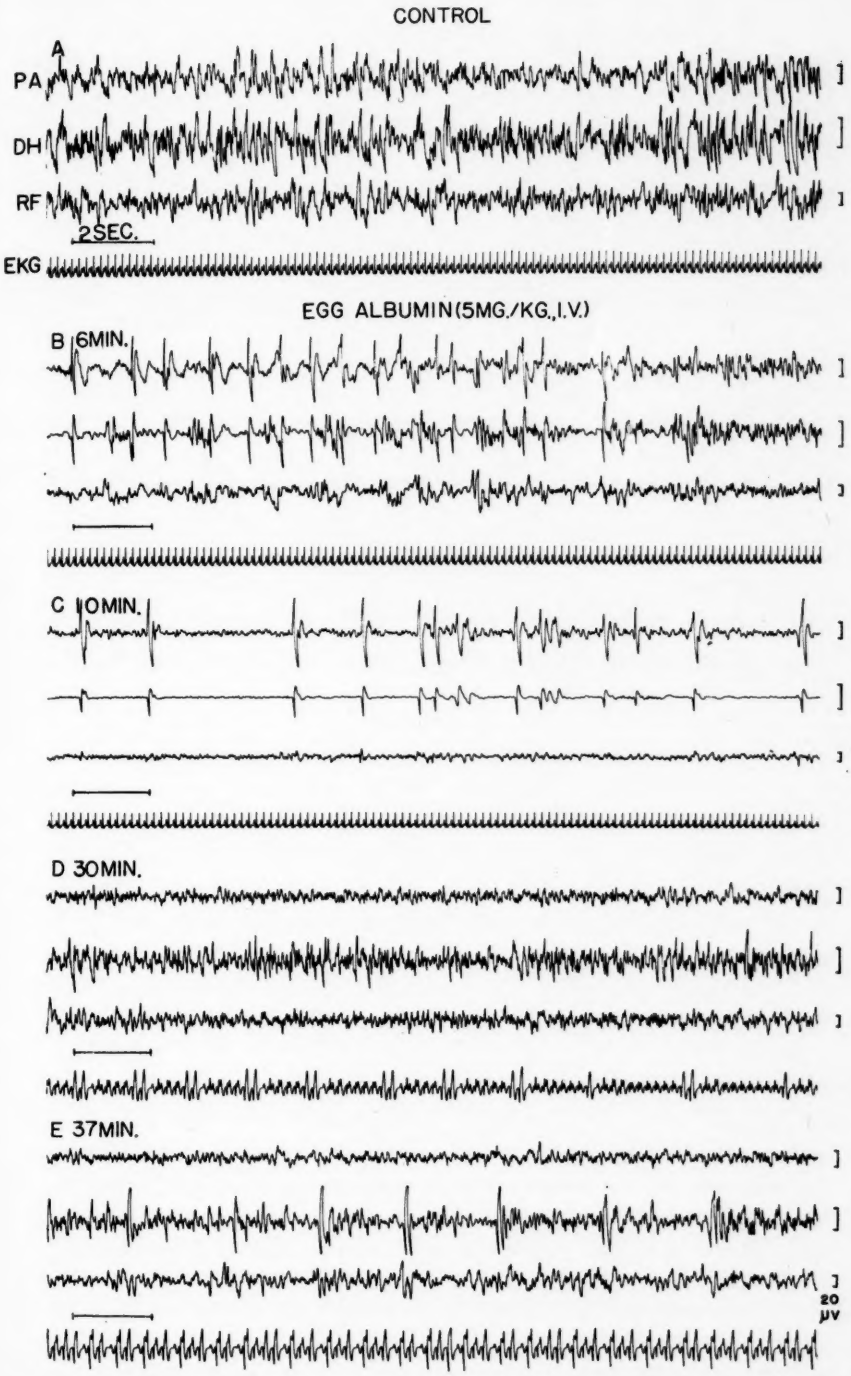

Fig. 2.—EEG and ECG recordings during typical anaphylaxis. *A*, control. *B*, *C*, *D*, *E*—6, 10, 30, and 37 min., respectively, after challenge. *PA* = Preoptic area. *DH* = Dorsal hippocampus. *RF* = Reticular formation.

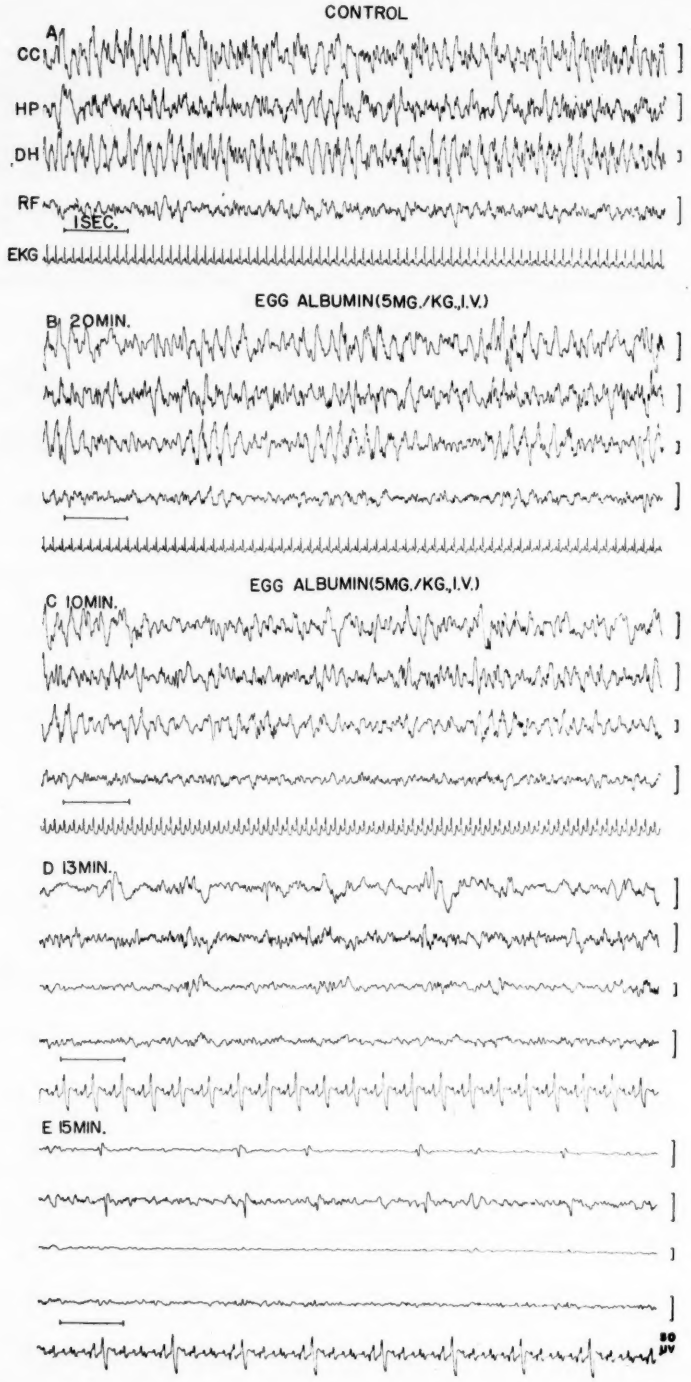

Fig. 3.—EEG and ECG recording during anaphylaxis in a resistant guinea pig. *A*, Control. *B*, 20 min. after initial challenge. *C*, *D*, *E*—10, 13, and 15 min., respectively, after a second injection given 30 minutes after the initial challenge. *CC* = Cerebral cortex. *HP* = Hypothalamus. *DH* = Dorsal hippocampus. *RF* = Reticular formation.

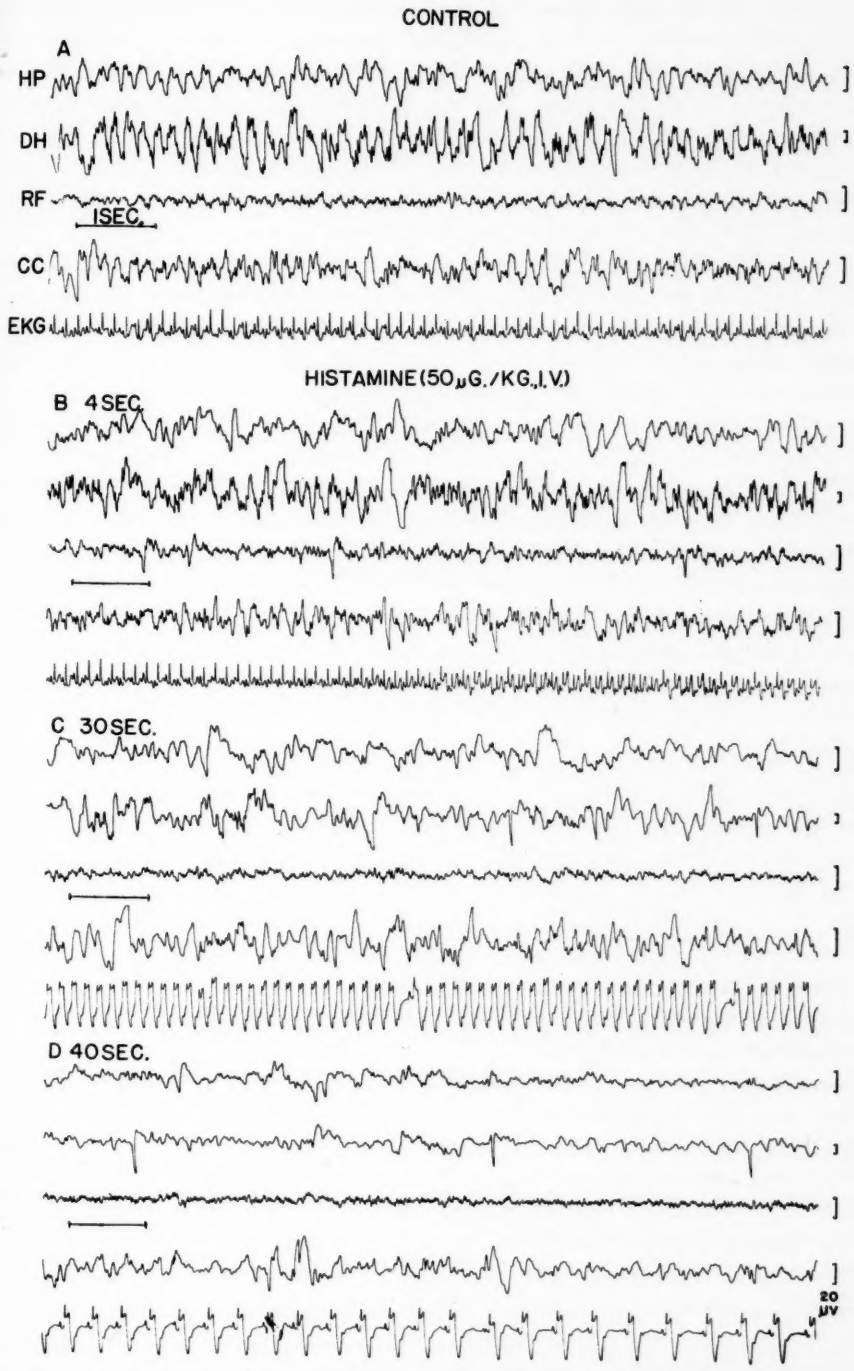

Fig. 4.—EEG and ECG recordings in a normal guinea pig after histamine injection. *A*, Control. *B*, *C*, *D*—4, 30, and 40 sec., respectively, after injection. *HP* = Hypothalamus. *DH* = Dorsal hippocampus. *RF* = Reticular formation. *CC* = Cerebral cortex.

until twenty-five to thirty seconds had elapsed (Fig. 4, *C*). At this time, the EEG started to become depressed with some spike activity evident in the hippocampus. The depressed state of the EEG was maintained for the next ten to twenty seconds (Fig. 4, *D*) and this was followed by gradual recovery with a return to the normal EEG and ECG occurring a short while later. With the exception that the ECG changes occurred before the changes in nervous activity and that the changes occurred more rapidly and with more rapid recovery, the results were very similar to those observed in anaphylaxis.

The marked bronchospasm produced by anaphylaxis and induced by histamine so readily in the guinea pig leads to ventilatory insufficiency and decreased blood oxygen saturation. As central nervous activity is readily modified by decreased oxygenation, the effects of simple asphyxia on nervous activity and the ECG were also observed. The changes recorded in both cases were very similar to those seen during histamine administration (Fig. 5) and (with the same exceptions noted above in the case of histamine) with those observed in anaphylaxis. As in the histamine experiments, ECG changes preceded those in the EEG. No modifications in nervous activity occurred until the heart rate had slowed to approximately 50 per cent of control values, at which time depression of nervous activity was observed (Fig. 5, *C*). Thereafter, both EEG and ECG activity deteriorated rapidly (Fig. 5, *D*).

In these four animals there was little or no biologic variability observed in the responses of the central nervous system.

DISCUSSION

The EEG effects observed in these studies concur in the main with those observed by Brandon.[6] We cannot, however, unreservedly agree with his conclusion that these represent specific physiochemical changes in or on the nerve cell proper induced by the antigen-antibody reaction. Local anaphylaxis as demonstrated in isolated guinea pig gut or uterus in the Schultz-Dale technique has long been cited as evidence for a specific cellular response to an immunologic anaphylactic stimulus, unmediated by humoral factors or total generalized physiologic response. However, in the study of central nervous activity in the intact animal, many problems arise in the differentiation of primary neurocellular effects from secondary phenomena dependent on total body economy. Central nervous activity has been shown to be dependent on many homeostatic mechanisms including oxygen and carbon dioxide equilibrium, circulatory stability, electrolyte balance, etc. Anaphylaxis produces profound changes in these factors, and it is, therefore, difficult to ascribe the changes in central nervous activity described above to neural anaphylaxis per se.

No clear-cut differences in pattern appear to exist between the changes observed in anaphylaxis, histamine injection, and asphyxia, the differences being of degree, duration, and time of onset in relation to ECG effects. Although the EEG changes appear before those of the ECG in anaphylaxis, and afterward in histamine and asphyxia experiments, this need not imply a specific antigen-antibody effect on the nerve cell. Histamine, various enzymes, and other

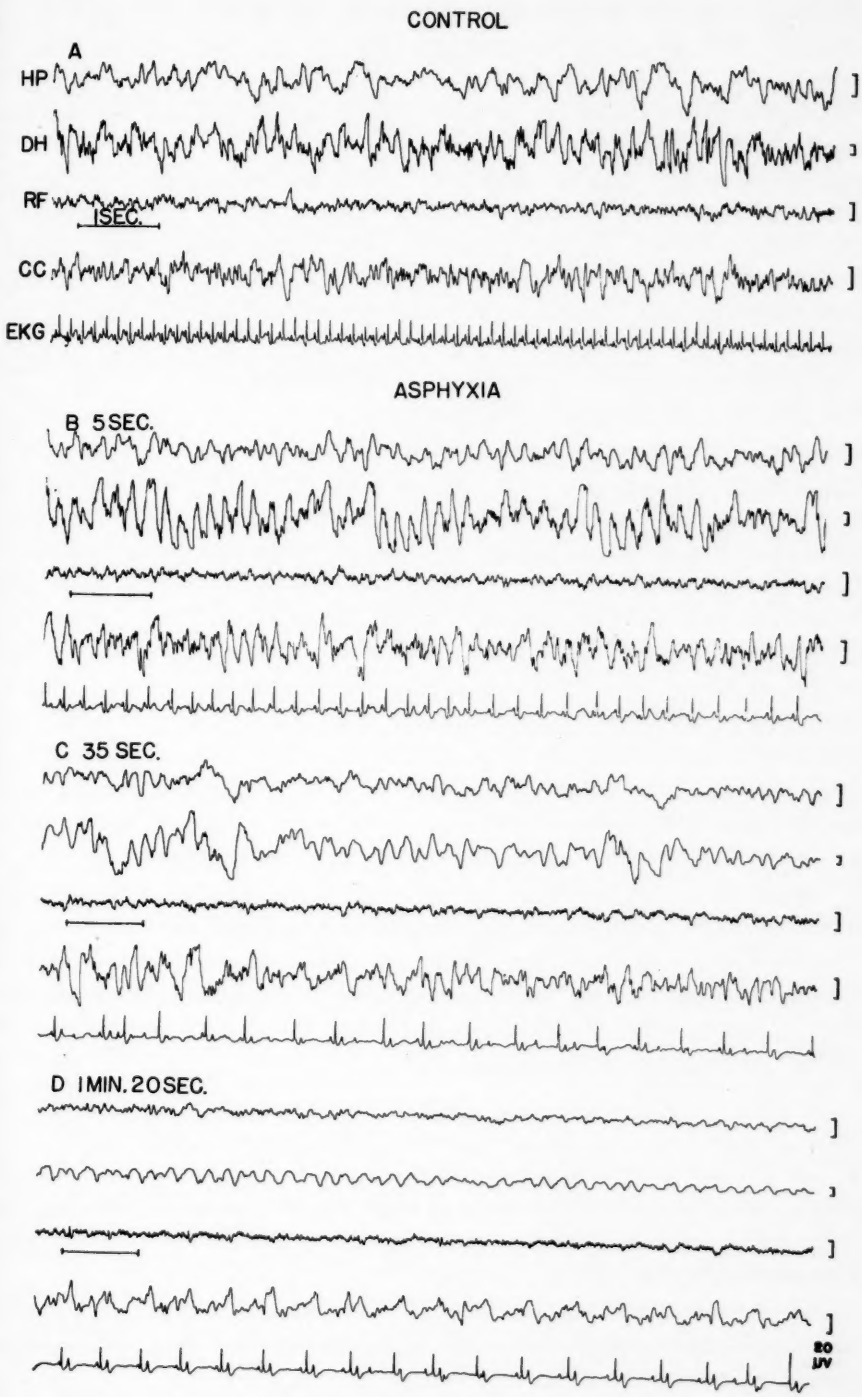

Fig. 5.—EEG and ECG recordings in normal guinea pig during asphyxia. *A*, Control. *B*, *C*, *D*—5, 35, and 80 sec., respectively, after suspension of artificial respiration. *HP* = Hypothalamus. *DH* = Dorsal hippocampus. *RF* = Reticular formation. *CC* = Cerebral cortex.

mediators are released, theoretically at all levels in the vascular tree during anaphylaxis. The early appearance of EEG changes may well represent central nervous reaction to release of these substances in the local blood supply, or to local vascular effects secondary to their release as conditioned by the high degree of sensitivity of neural tissue.

Additional studies will be needed to clarify the role of such physiologic changes as decreased oxygenation, decreased blood pressure, increased hematocrit and decreased blood volume, extracellular electrolyte shifts, and circulatory failure in the production of central nervous effects, with or without anaphylaxis. Pharmacologic studies of the effects of enzymes and mediators released in anaphylaxis on central nervous activity will also be needed to clarify the role of neuroanaphylaxis per se on the observed central nervous activity effects.

The area studied showing the highest reactivity in these studies, the dorsal hippocampus, is known to have an unstable blood supply and to be sensitive to factors affecting this supply.[8, 9] It exhibits high levels of reactivity and instability in general. The converse is true for the level showing the least reactivity, the midbrain reticulum, for this is known to be a very stable area.[10-14] Therefore, these regional differences in reactivity observed in anaphylaxis, histamine injection, and asphyxia appear to reflect pre-existing factors rather than any specific shift in reactivity related to the anaphylactic state itself.

In contradistinction to the extirpation experiments previously cited, we have been unable to demonstrate any areas of specific anaphylactic reactivity in the central nervous system, perhaps because the hypothalamus and the midbrain reticulum may not be primary centers of elaboration of anaphylactic response, but simply important afferent and efferent pathways for the complex system of neurovegetative and adaptive reflexes involved in those responses.

It should be emphasized that species specificities play an important role in neurophysiology in general and in anaphylaxis in particular. It would be of particular interest to corroborate the present EEG findings in a species, such as the rat, exhibiting less dramatic bronchospasm or disturbances of total body economy in anaphylaxis. Certainly caution is necessary in extrapolation of data in the guinea pig to other species.

SUMMARY

1. The changes in central nervous activity observed in the guinea pig during anaphylaxis, histamine injection, and asphyxia were characterized by high amplitude spike activity, flattening of background activity, desynchronization, and high amplitude slow waves.

2. Pronounced disturbances in electrical activity are recorded in the cerebral cortex, dorsal hippocampus, preoptic area, and hypothalamus. These occur to a markedly lesser extent in the midbrain reticulum.

3. These disturbances in electrical activity indicate that irritative mechanisms exist in the central nervous system during anaphylaxis.

4. The data suggest that these irritative mechanisms are not confined to specific regions in the central nervous system and may be the result of generalized phenomena.

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PEPTONE SHOCK IN THE PERTUSSIS-SENSITIZED MOUSE

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IT IS now well established that the susceptibility of white mice to the lethal effects of histamine and serotonin is enhanced by the intraperitoneal injection of *Hemophilus pertussis* phase I vaccine.[1-3] This effect is not believed to be a result of general debilitation for such mice do not show a heightened response to tuberculin,[4] epinephrine,[5] carbaminocholine,[5] Compound 48/80,[6] heterologous sera or proteins,[4] etc. In addition to these, our preliminary studies indicated that the pertussis-inoculated mouse was not sensitive to the intravenous administration of the specific peptone, Bacto-Peptone.

Intravenously injected peptone in the dog, rabbit, guinea pig, etc., results in a state of vascular collapse resembling histamine shock and is believed to be a consequence of the actual liberation of endogenous histamine in those species.[7] Since the mouse is not only incapable of storing and, hence, releasing appreciable amounts of histamine[8] but is also inherently relatively insensitive to histamine,[1] the above results with peptone were not entirely unexpected. However, following these observations, a report[9] appeared which indicated that prior treatment with pertussis did indeed create a state of heightened response to peptone. Because the results with Bacto-Peptone could be confirmed in this laboratory, the subsequent studies were carried out with a series of peptones.

MATERIALS AND METHODS

Female, Swiss-Webster white mice of about 18 to 20 grams in weight, obtained from Tumblebrook Farm, were used in these experiments. In so far as possible the technical procedures which were followed were those of Hunder and Spink.[9] Each mouse received an intraperitoneal injection of 0.5 ml. of a standardized *H. pertussis* phase I vaccine containing 6×10^9 organisms. A 30 per cent suspension in distilled water of each of the following peptone preparations was autoclaved and kept at 4° C. prior to use: (a) *Peptonum Siccum* nach, *Witte,* (b) Bacto-Peptone (Difco), (c) Proteose-Peptone (Difco), (d) Proteose-Peptone No. 2 (Difco), (e) Proteose-Peptone No. 3 (Difco), (f) Bacto-Protone (Difco), (g) Neopeptone (Difco), (h) Bacto-Tryptone (Difco), (i) Tryptose (Difco), (j) bacteriological peptone (Nutritional Biochemicals), (k)

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peptone "I" (Nutritional Biochemicals), and (l) peptone "S" (Nutritional Biochemicals). On the sixth day subsequent to the inoculation with pertussis vaccine, each mouse received 0.5 ml. of one of the above suspensions given intraperitoneally. About 150 mg. of peptone was thus injected.

RESULTS

Following the challenge inoculation all animals showed some signs of reaction such as lethargy, shallow and/or forced respirations, ruffling of the fur, edema of the paws and snout, rubbing of the snout, scratching of the skin, cyanosis, etc. Convulsions, if they occurred, were indicative of eventual death although not all animals that died exhibited this response. These described reactions, which are typical for mice in anaphylaxis, are also seen following histamine and serotonin administration. Death of the mouse within twenty-four hours after the challenge inoculation was chosen as the criterion for profound susceptibility to peptone; all other reactions were disregarded. These mortality results, number of animals dead/number of animals challenged, are shown in Table I. Our initial observations, that pretreatment of the mouse with pertussis vaccine did not result in an altered sensitivity to Bacto-Peptone,

TABLE I. PEPTONE SHOCK IN PERTUSSIS-SENSITIZED MICE

PEPTONE 150 MG. (INTRAPERITONEALLY)	MORTALITY RATE	
	CONTROL (UNTREATED)	*H. pertussis* (6 DAYS PRIOR)
Bacto-Peptone	0/20	0/29*
Bacteriological peptone (Nutritional Biochemicals)	0/8	3/10
Witte's peptone	1/15	9/25
Neopeptone	5/10	10/13
Bacto-Tryptone	1/10	11/14
Proteose-Peptone No. 3	0/10	11/13
Proteose-Peptone	3/22	29/31
Tryptose	3/6	6/10
Peptone "S"	3/6	7/10
Proteose-Peptone No. 2	8/10	11/13
Bacto-Protone	8/10	12/14
Peptone "I"	5/6	6/10

*Mortality rate = number dead/number injected.

were confirmed. On the other hand, sensitization to Proteose-Peptone did occur, as reported previously.[9] Of the other peptones studied, Proteose-Peptone No. 3 and Bacto-Tryptone were also found to be markedly lethal to pertussis-treated animals. Several of the peptone preparations such as peptone "I," peptone "S," Neopeptone, and Bacto-Protone were toxic to control animals in the amounts given so that no conclusions could be drawn on the effects of prior vaccination with pertussis. Witte's peptone, bacteriological peptone (Nutritional Biochemicals), and Neopeptone gave intermediate results, i.e., less than 50 per cent mortality in the pertussis-vaccinated mice.

DISCUSSION

The similarity observed between anaphylaxis and peptone shock in certain species is reflected by the toxins or biologically active mediators released, that

is, histamine, serotonin, heparin, bradykinin, etc., and, perhaps, other slowly reacting substances.[7] The mouse (and rat), however, presents a unique situation in that this animal is relatively insensitive to the lethal effects of exogenous histamine and serotonin, per se, or to the endogenous release of these and other substances following anaphylactic and peptone shocks. Although the resistance to these agents is markedly decreased by prior sensitization with pertussis vaccine, it is not likely that fatal anaphylaxis or peptone shock is the result, solely, of the release of these mediators. The following aspects should be considered: The mouse does not have a store of readily available histamine and it has been said[8] that, even if all the stored histamine could be released simultaneously, it would not be of sufficient quantity to be lethal. Pretreatment with *H. pertussis* phase I vaccine diminishes the resistance of mice to histamine by about fiftyfold.[1] Even under these circumstances, the LD_{100} for a 20 gram mouse is relatively high, being approximately 200 γ of histamine as the base inoculated intraperitoneally.[4] In addition, it should be emphasized that the potent histamine-releasing agent, Compound 48/80, apparently is not capable of mobilizing at once the LD_{100} of histamine, for Compound 48/80 is not lethal even to pertussis-treated mice.[6]

The differences in activity of the various peptone preparations is not unexpected. Peptones are usually prepared by the enzymatic degradation of proteins from different sources. The type of enzyme, protein substrate, length of digestion, temperature, etc., required for the process characterizes the peptone. The hydrolysis which results from enzymatic digestion in the preparation of peptone may be accompanied by decarboxylation and result in the formation of toxic amines. Indeed, it is assumed that histamine-like substances (if not histamine itself) are usually present in amounts varying with the different preparations of peptone.[10] The histamine content as base/gram* for several peptones utilized in this study was as follows: Proteose-Peptone, 180 γ; Witte's peptone 136 γ; and Bacto-Peptone 16 γ, respectively. As might be expected, the peptone containing the greatest amount of histamine (Proteose-Peptone) displayed the greatest relative reactivity in the pertussis-sensitized mouse, i.e., a high mortality rate was obtained (see Table II). Witte's peptone, containing an intermediate amount of histamine, was only moderately lethal while Bacto-Peptone, with the least quantity of histamine, was not at all lethal to pertussis-treated mice. The maximum quantity of histamine delivered to the mouse in 150 mg. of Proteose-Peptone is only about one tenth the intraperitoneally injected LD_{100} for the histamine-sensitive mouse.

TABLE II. RELATIONSHIP OF HISTAMINE AND SEROTONIN CONTENT TO MORTALITY

PEPTONE	HISTAMINE (γ/GM.)	SEROTONIN (γ/GM.)	MORTALITY IN PERTUSSIS-VACCINATED MICE
Bacto-Peptone	16	<10	0/29
Witte's peptone	136	<10	9/25
Proteose-Peptone	180	<10	29/31

*We are indebted to Dr. Floyd C. McIntire of Abbott Laboratories, North Chicago, Ill., for the determinations of histamine.

The pertussis-inoculated mouse also exhibits an increased sensitivity to 5-hydroxytryptamine (serotonin)[3, 4]; the content of 5-hydroxyindole for the above three peptones was found to be < 10 γ per gram each,* indicating that the contained serotonin was not an important factor in the death of the animal.

Peptone is reported as causing mast cell disruption in the mouse.[11] Since mouse tissues are very rich in mast cells, being present in loose connective tissue and along the lymphatic channels, small blood vessels and nerves of the lung, mesentery, intestine, etc., destruction of many of these cells would release appreciable quantities of serotonin as well as histamine, heparin, etc. The LD_{50} of serotonin for the pertussis-inoculated animal is about 2 to 6 γ per gram of mouse.[2, 3] A lethal quantity of serotonin from disrupted mast cells would be reflected by the presence of its metabolic products such as urinary 5-hydroxyindole acetic acid. However, none of the latter was found in urine collected from a group of mice over a 24-hour period after peptone administration. It is probably unlikely, therefore, that the mechanism of death from peptone is a result of the serotonin released from mast cells.

It is apparent from the above observations that there is no one mechanism which can account for the lethal effects of peptone in the pertussis-sensitized mouse. In addition to the toxic substances, possibly administered together with the peptone, and the mediators released by its stimulation one must take cognizance of the unknown factors present in peptone, perhaps, capable of causing the release of or activation of a lethal factor. The enzyme systems need be considered in this regard. Rather than considering a single entity, it is more than likely that the circumstances leading to a fatal outcome are an accumulation of several of these factors. The mouse deserves special consideration because of its inherent resistance to histamine and serotonin and the resemblance of the shock state whether due to histamine, serotonin, peptone, or anaphylaxis.

SUMMARY

The susceptibility of pertussis-sensitized mice to fatal shock varies with each peptone preparation. The peptone containing the greatest amount of histamine produced the highest mortality rate. It was confirmed that Bacto-Peptone, with relatively little histamine content, was without appreciable effect. The mechanism of death is probably neither the exogenous histamine administered nor the histamine or serotonin engendered but a combination of these and other factors, still unknown.

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ANAPHYLACTIC REACTION IN TUMOR-BEARING (MASTOCYTOMA) MICE

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THE MAST CELL of tissues of the experimental animal has been accepted as a source of 5-hydroxytryptamine (serotonin)[1] as well as being a reservoir for histamine, heparin, etc. The widespread degranulation of local tissue mast cells seen to follow injection of antigen into sensitized mice[2] suggests that these cells participate in the anaphylactic reaction by release of these mediators. However, an uncertainty concerning the causal relationship exists, for it has been noted that anaphylactic shock is little altered by previous depletion of histamine and serotonin from the tissues.[3] The concurrent sensitization of the mouse to the lethal effects of histamine[4] and anaphylaxis[5] by inoculation with *Hemophilus pertussis* phase I organisms has led to speculation concerning the interdependence of these phenomena.[6] The subsequent finding[7, 8] that the pertussis-inoculated mouse possesses a concomitant sensitivity to serotonin has added the latter as another agent participating in anaphylaxis. Availability of a mouse-transferable mastocytoma, potentially capable of secreting large amounts of histamine and serotonin,[9] provided the opportunity of observing the effect of pertussis-inoculation and subsequent challenge on the structure of the mast cell.

MATERIALS AND METHODS

Mice.—Adult, female mice of the LAF_1 strain, weighing about 15 to 18 grams, at the start of the experimental study, were each inoculated intraperitoneally with a saline suspension of homogenized mastocytoma.

Assay.—Starting about thirty days after inoculation with tumor, assays of urinary 5-hydroxyindoleacetic acid (5-HIAA) were carried out periodically on these animals. The pooled urine samples collected over a 24-hour period from groups of four to five mice in a fasting state were analyzed for 5-HIAA by the technique of Sjoerdsma and co-workers.[10] This procedure was made semiquantitative by reading in the Beckman spectrophotometer at 540 mμ against a standard. This technique is reliable as a screening procedure since presence of

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an actively growing tumor is accompanied by liberation of relatively large amounts of serotonin and, hence, excretion of large amounts of 5-HIAA. The average amount of 5-HIAA excreted in 24 hours was calculated as gamma per mouse. About 50 per cent recovery of exogenously administered serotonin as urinary 5-HIAA is possible by this technique.

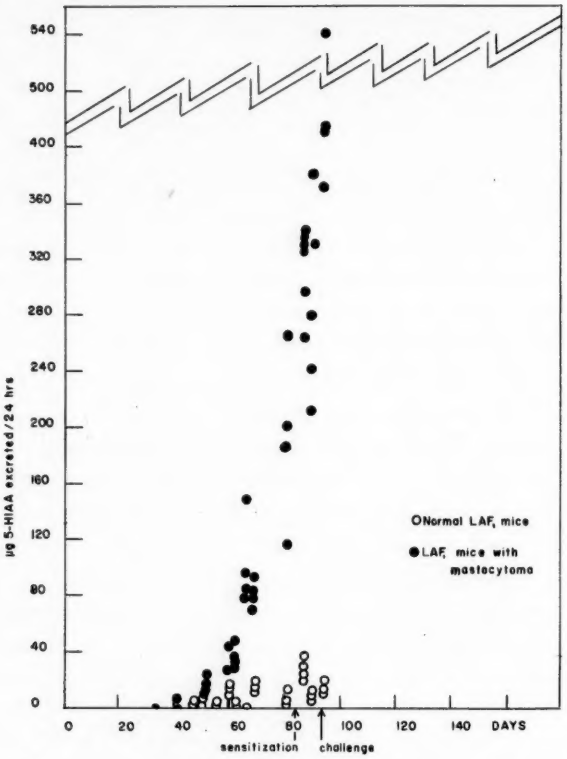

Fig. 1.—5-HIAA excretion in mastocytoma-LAF_1 mice.

Sensitization.—Each mouse was inoculated intraperitoneally with 6×10^9 *H. pertussis* phase I organisms on the eighty-fourth day following transplantation of tumor. By this time a marked increase in urinary 5-HIAA excretion had taken place (Fig. 1), usually coinciding with appearance of ascites and/or palpable tumor. Control mice received the vaccine only.

RESULTS

Histamine Sensitivity.—On the fourth day after inoculation with pertussis, each mouse of the following groups received 0.036 mg. histamine phosphate per gram of body weight intraperitoneally as a 0.2 per cent solution: (1) Swiss-Webster mice (control), (2) pertussis-inoculated Swiss Webster mice (control), (3) LAF_1 mice (control), (4) pertussis-inoculated LAF_1 mice, (5) tumor-bearing LAF_1 mice, and (6) pertussis-inoculated tumor-bearing LAF_1 mice. The results as seen in Table I indicate that neither pertussis-inoculated LAF_1

mice nor LAF_1 mice with actively growing tumor display any significant enhancement of sensitivity to histamine.

TABLE I. REACTION OF TUMOR-BEARING MICE TO HISTAMINE AND SEROTONIN

CHALLENGE (DAY 4 AFTER SENSITIZATION)	SENSITIZATION OF MICE					
	SWISS-WEBSTER		LAF_1		LAF_1-TUMOR*	
	CONTROL	*H. pertussis*	CONTROL	*H. pertussis*	CONTROL	*H. pertussis*
Histamine Phosphate (mg./Gm. mouse)						
0.036	0/10†	5/10	0/10	0/6	0/12	0/6
.072				0/2		
.108				0/4		
.126				2/4	0/4	1/4
Serotonin (mg./Gm. mouse)						
0.05	0/4	5/5	0/5	5/5	0/4	

*Bearing palpable, actively secreting mastocytoma.
†No. dead/No. challenged.

Serotonin Sensitivity.—On the fourth day after the pertussis inoculation, each of the mice similarly prepared as in the first five groups described for histamine received 0.050 mg. serotonin per gram of body weight intraperitoneally as a 0.2 per cent solution. The results (Table I) indicate that pertussis inoculation sensitizes LAF_1 as well as Swiss-Webster mice to the lethal effects of exogenous serotonin. Pertussis inoculation failed to sensitize tumor-bearing mice to their own endogenously released serotonin. No higher incidence of deaths was noted over a thirteen day span following inoculation as compared to tumor-bearing mice not receiving the pertussis.

Anaphylaxis.—On the tenth day after inoculation with a mixture containing 6×10^9 *H. pertussis* organisms and 0.1 ml. horse serum given intraperitoneally each mouse of groups identical to the above was challenged by either 0.01 or 0.1 ml. horse serum given intravenously. The results, expressed as number of animals dead of anaphylactic shock/number of animals challenged (Table II), indicate that (a) the LAF_1 strain of mouse can be effectively sensitized by use of pertussis vaccine, (b) presence of an actively growing mastocytoma does not cause an enhancement of anaphylactic sensitization, and (c) the mastocytoma does not alter incidence of anaphylactic deaths as compared to either LAF_1 or Swiss-Webster controls.

TABLE II. ANAPHYLACTIC SENSITIVITY OF TUMOR-MICE

CHALLENGE (DAY 10 AFTER SENSITIZATION)	SENSITIZATION OF MICE					
	SWISS-WEBSTER		LAF_1		LAF_1-TUMOR*	
	CONTROL H.S.†	*H. pertussis*-H.S.	CONTROL H.S.	*H. pertussis*-H.S.	CONTROL H.S.	*H. pertussis*-H.S.
Horse serum (intravenously)						
0.1 ml.	0/10‡	9/10	1/5	3/5	0/5	4/5
0.01 ml.			0/10	3/7	1/12	9/15

*Bearing palpable, actively secreting mastocytoma.
†Horse serum.
‡No. dead/No. challenged.

Histologic Study.—Sections of tumor from animals of each of the following groups were fixed in formalin and stained with hematoxylin and eosin: (1) Control, receiving no treatment; (2) intraperitoneal horse serum, thirteen days prior to sacrifice; (3) intravenous horse serum challenge ten days after prior intraperitoneal horse serum, surviving shock; (4) same treatment as in previous group but dying in shock; (5) intraperitoneal pertussis and horse serum thirteen days prior to sacrifice; (6) intraperitoneal pertussis and horse serum, death by histamine on the fourth day; (7) intraperitoneal pertussis and horse serum ten days prior to intravenous challenge with horse serum, surviving, and (8) same treatment as those in previous group but dying in shock. In no case was the architecture of the tumor altered by the treatment. The tumor consists essentially of a sea of uniform appearing cells, generally small, with large vesicular nuclei and clumped chromatin. The cytoplasm is scant and moderately eosinophilic and contains a centrally located nucleus. With this stain, the cells resemble the lymphocytic-plasma cell series with no cytoplasmic granules. The tumor is moderately vascular and has a very thin, light, fibrous connective tissue stroma.

DISCUSSION

From previous studies[11] it can be stated that histamine actually plays a relatively minor role in anaphylaxis in the mouse. This conclusion seems warranted even though pertussis inoculation engenders an enhancement to both histamine and anaphylactic shock. The implication of serotonin as a mediator in the latter reaction, in part, arises from the simultaneous enhancement of its lethal effect in pertussis-treated mice.[7, 8] In addition, the following observations stress its role: anti-serotonin agents inhibit the uterine reaction in sensitized mice,[12] mast cells disrupt and discharge their granules in response to an antibody-antigen reaction,[2] tissue serotonin is depleted following disruption of such cells,[13] serotonin accumulates in the lungs of certain animals in anaphylactic shock,[14] etc.

Although these observations seem to strengthen the role of the mast cell and serotonin in reactions of hypersensitivity, anaphylaxis apparently can take place fully as effectively in the pertussis-vaccinated mouse at a time when serotonin hypersensitivity has disappeared.[15] Then, too, little alteration of shock was evident in rats depleted of skin and intestinal serotonin or treated with specific serotonin antagonists.[3]

Because of these varied observations, it became desirable to observe the anaphylactic reaction in mice under the influence of a tumor capable of secreting large amounts of serotonin. Inoculation with *H. pertussis* enhances the sensitivity of mice to exogenously administered serotonin, maximum sensitivity being attained about five days after treatment. Although the mastocytoma maintains a continuous secretion, pertussis inoculation was found to be without effect in engendering toxic reactions to this endogenously released serotonin over the course of the experiment. Possible explanations are (a) the amine as secreted in the native state is physiologically inactive by being in the bound

state, (b) inhibitory substances are present in the blood which equilibrate the activity, and (c) a resistance or tolerance is built up as the secretion progresses. The unavailability of the secretion to specialized sensitized sites should be considered, also, although serotonin is found in the blood.

The high concentration of 5-HIAA recovered in the urine, a direct reflection of the amount of serotonin secreted, indicates a high degree of activity of the tumor mast cells. If an enhancement of serotonin secretion resulted from the antibody-antigen reaction, the increment was not of sufficient magnitude to influence the 5-HIAA determination. No change in the integrity of the microscopic structure of the mastocytoma results from the anaphylactic reaction. Either the mast cells do not respond to the reaction, as has been observed elsewhere, or the reagents and/or the reaction products cannot penetrate the tumor to affect its cells.

As has been found previously with CF-1 mice,[8] it has been here ascertained that the LAF_1 strain of mouse does not become highly sensitive to histamine after injection with pertussis. However, in both of the above strains the reaction to serotonin is enhanced and anaphylactic sensitivity is engendered by pertussis treatment. Although this may appear to indicate that serotonin is of direct significance in anaphylaxis, it has been shown with CF-1 mice that the latter reaction takes place in absence of serotonin sensitivity[15] depending on the time interval following pertussis administration. The events occurring in this time interval bear investigation.

Parfentjev[16] has reported that the presence of actively growing Sarcoma 180 sensitizes mice to histamine as does pertussis inoculation. No such effect was produced by the mastocytoma; it itself was without influence and its presence failed to augment the result of pertussis inoculation.

SUMMARY

Large amounts of 5-HIAA are found in urine of mice with an actively growing mastocytoma. This tumor, secreting serotonin in relatively large amounts, was no more lethal to pertussis-inoculated mice than it was to uninoculated control animals. Presence of the tumor was without effect on anaphylactic reaction or on sensitivity to histamine and serotonin. The LAF_1 strain of mouse becomes sensitive to serotonin but not to histamine following pertussis treatment.

We are indebted to Dr. Jacob Furth of the Children's Medical Center, Boston, for having made available the LAF_1 mice and the transferable mastocytoma.

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CARDIAC ASTHMA—A MISNOMER

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In 1929, Palmer and White[1] in a paper entitled "The Clinical Significance of Cardiac Asthma" reported the results of their studies of 250 patients with "cardiac asthma." According to their definition, originally introduced into English medicine by Hope[2] as early as 1832, cardiac asthma is a "paroxysmal acute dyspnea, generally occurring at night but sometimes following exertion, lasting from minutes to hours and accompanied by a sense of suffocation, by wheezing and often by cough with frothy sputum, which may or may not be bloody, and which is due fundamentally to serious heart disease, especially involving the left ventricle. The attack is characteristically relieved by the upright position and by morphine. On physical examination, wheezing respirations and sometimes moist rales are observed." In this article, White apparently used the response to morphine as a criterion of whether the asthma was bronchial or cardiac in origin.

In 1932, in a second paper entitled "A Follow-Up Report on the Clinical Study of 250 Cases of Cardiac Asthma," McGinn and White[3] noted after a 3-year follow-up study of these patients that, "We are making a further study of the incidence of bronchial asthma and of other allergic manifestations in individuals with cardiac asthma and in their families. We have noted the coincidence a number of times but have not completed a careful analysis."

These articles, which seemed to delineate cardiac asthma as a distinct entity, so impressed the senior author that in the first edition of his book *Clinical Allergy*,[4] published in 1937, he included "cardiac asthma," as part of the general classification of asthma, and defined "cardiac asthma," as interpreted from White's article, as follows: "a paroxysmal type of dyspnea accompanied by wheezing respirations coming on usually at night in people past middle life with sudden relative failure of left ventricle, usually of hypertensive etiology, showing a poor therapeutic response to adrenaline vs. a good response to morphine."

As an example of true "cardiac asthma" corresponding to this description, the senior author included the following case report which in all its details seemed to fit the definition.

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CASE 1.—Mrs. E. E., fifty-five years of age, was admitted to the hospital on Nov. 5, 1936, with a history of paroxysmal attacks of a nocturnal wheezing type of dyspnea, interpreted as "asthma" by the patient, beginning on Aug. 23, 1936, and recurring almost daily since that time. Attacks wakened the patient out of sleep, lasted a short period of time, and disappeared by morning. Epigastric pain and vomiting occurred occasionally in association with the attack. The patient had frequent headaches. The personal and family history were negative for allergy.

Upon physical examination at the time of admission, the patient showed marked orthopnea and occasional Cheyne-Stokes breathing, slight cyanosis, moderate liver enlargement, and a few râles at the base of the right lung posteriorly. The pulse was 104 and regular. Blood pressure: right arm 175/90 and 150/110 mm. Hg; left arm 150/115 and 155/115 mm. Hg. The heart was enlarged slightly to the left, gallop rhythm was present, and there was a double murmur at the apex and a diastolic murmur at the aortic area. The electrocardiogram showed sinus rhythm, intraventricular block of high degree, and prolongation of ventricular systole.

X-ray examination showed the following: "The cardiac silhouette is larger than normal. The configuration indicates that this enlargement is limited largely to the left ventricle. The lateral view shows the encroachment on the retrocardiac space by the enlarged left ventricle. Moderate accentuation of the vessel tree markings is noted."

The clinical diagnosis made at that time was as follows: (1) Severe organic disease (hypertensive and atherosclerotic type) with myocardial fibrosis and (2) cardiac asthma.

Treatment which consisted primarily of rest and the administration of aminophylline was followed by considerable improvement in the asthmatic symptoms.

Here then was what seemed at that time to be a typical case of "cardiac asthma"—a patient with paroxysmal nocturnal attacks of wheezing which were not distinguishable in their physical characteristics from ordinary asthma. The recent onset of the asthma, the age of the patient, the unmistakable signs of organic heart disease, especially the marked hypertrophy of the left ventricle, all pointed to a cardiac basis for the asthma as indicated in White's definition. This idea was so fixed in our minds that little effort was made to find by additional history or allergy tests whether the patient at one time might have had allergic or bronchial asthma which was so overshadowed by the cardiac findings as to obscure it completely.

With this patient acting as a prototype of typical "cardiac asthma," the senior author began to look for similar cases. But strangely enough, over the ensuing period of nearly twenty-five years, he has been unable to find any similar cases which also fitted the original description of "cardiac asthma." This seemed even more puzzling when we were told by many cardiologists and internists that, in their experience, cardiac asthma was a fairly common disorder. Closer investigation of those patients referred to us for what was regarded as cardiac asthma showed that such patients actually had an underlying bronchial asthma and also happened to have associated cardiac difficulties. If this were true and could be confirmed by further study, then the designation "cardiac asthma" should be considered a misnomer and should be dropped from our present nomenclature and from our classifications of asthma. Of even greater significance was the necessity to make a clear-cut differentiation in clinical practice. Thus, if a patient with bronchial asthma also has unrelated cardiac difficulty which is causing no immediate symptoms (as, for example,

mild hypertensive heart disease), the treatment of such a patient would be different from that given to a patient who has organic heart disease, perhaps with failure, and at the same time has an associated bronchial asthma.

Not only are cardiologists and internists confused about the differentiation but even those allergists who have written about "cardiac asthma" in recent years are not very clear about it. Thus, for example, Swineford, who has written extensively about cardiac asthma,[5, 6, 7] classifies these patients into those having paroxysmal cardiac dyspnea and no asthma and into a second group designated as having cardiac asthma in which both cardiac disease and asthma were present. In his most recent publication[8] (1958), he observed that asthma may coexist with heart disease and run an independent course. He noted, however, that of 26 patients with "cardiac asthma," twenty were greatly relieved by combined cardiac and allergy care. Even White[9] is not too clear about the differentiation since, in the last edition of his book, *Heart Disease*, published in 1951, he stated that "cardiac asthma is merely bronchial asthma due to bronchiolar spasm added to and set off by heart failure in an 'asthmatic type' individual." Despite this statement by White, the term "cardiac asthma" continues to appear in various text books and publications and is used in clinical practice by many practitioners.

It seemed to us that much of the confusion about "cardiac asthma" could be dispelled and clarified by an investigation designed to determine more definitely whether "cardiac asthma" does exist as a separate and distinct clinical entity separate from bronchial asthma. We felt that this could best be accomplished in two ways: (1) By an investigation of patients with both asthma and coexistent cardiovascular disease (hypertensive or arteriosclerotic, with or without coronary involvement) to determine whether their asthma was bronchial (or allergic) or cardiac in origin. Special attention was to be given to those patients who previously were regarded as having "cardiac asthma" or in whom the cardiac condition was considered the major cause of their asthma. (2) By the study of a similar control group of patients who had organic heart disease only, preferably of the hypertensive and/or coronary types, to see whether they had asthma or even the wheezing type of respiration usually associated with asthma. We reasoned that if heart disease per se was an important or frequent cause of asthma, one should find it fairly often in patients in whom left ventricular failure was common, especially as a terminal event.

METHODS OF STUDY

The material making up the first group, namely, cases of asthma and coexistent cardiovascular disease, was composed of those patients seen at the office of the senior author and a few additional ones seen at Temple University Medical Center.* Only those patients from the Outpatient Allergy Clinic were included whose asthma had been considered to be of cardiac origin and managed

*Any mention of hospital or of outpatient clinics in subsequent case reports refers to Temple University Medical Center or to the Allergy Outpatient Clinic of its Hospital.

as such. The case records of these patients were reviewed in detail and included a careful history of the duration of wheezing and its relation both to the existing cardiac disease and to the onset of cardiac failure. The duration of the asthma was especially significant since, according to White, the onset of asthma in the cardiac types was a bad prognostic omen which indicated a fatal outcome often in less than a year and not more than 1.4 years on the average. The response to various drugs utilized in treatment (such as, epinephrine, aminophylline, digitalis, opiates, etc.) also was noted. Attempts were made to determine the bronchial or allergic character of the asthma by a history of other allergies either in the patient or his family, the results of allergy tests, and the findings by special examinations (bronchoscopic, blood tests for eosinophilia, etc.). Finally, evidence of organic cardiovascular disease manifested by abnormalities in blood pressure, electrocardiogram, roentgenograms, circulation time, venous pressure, etc., was looked for, as well as evidence of cardiac insufficiency (edema of legs, pulmonary or hepatic congestion, etc.).

The material included in the second or control group was obtained by a survey of the hospital records of patients selected at random from the files of our hospital record room. These patients had been admitted to the hospital because of cardiovascular disease which was often associated with failure and listed in the final records as "heart disease, hypertensive and/or coronary disease." Due care was exercised to use only those cases in which there were complete histories and examinations, both clinical and laboratory. These records then were reviewed for evidence of a past history of attacks of wheezing respiration or actual asthma, a family history of allergy, and any indication, either from the present history, from examination of the chest, or from laboratory examinations (such as, for eosinophilia) that the condition might be allergic.

RESULTS

All of the 103 patients comprising the first group had coexistent cardiac disease (mostly hypertensive) and allergic bronchial asthma. Except for Case 1, seen originally in 1936 and already reviewed, none of the patients, with possibly one exception, presented a picture so typical of so-called "cardiac asthma" as to make differential diagnosis of bronchial asthma difficult. The exception was a patient seen in the private office of the senior author whose case history follows.

CASE 2.—M. H., male, aged sixty-seven, had recurrent attacks of nocturnal dyspnea and wheezing of about four years' duration which were relieved by Tedral and by a nebulizer. His sister had asthma; a niece migraine. Because of the presence of exertional dyspnea and slight ankle edema, his condition was considered to be of cardiac origin by his attending physician and he was given digitalis, Diuril, and Hydrodiuril with only slight relief. When seen by the senior author, physical examination showed a blood pressure of 170/90 mm. Hg, slight cyanosis, marked emphysema of the chest with a slight but definite asthmatic wheeze throughout the chest. The patient had cardiac enlargement in moderate degree, especially to the left side, and a blowing systolic murmur over the entire precordium. X-ray study of

the heart showed moderate, generalized enlargement with left ventricular preponderance, also a large and tortuous aorta. The lungs showed minimal pleural reaction, probably old pleural thickening at the right base, and considerable increase in the anteroposterior diameter of the chest. Intracutaneous skin test reactions to house dust and to feathers were positive.

The patient was placed on an allergy elimination diet and was given potassium iodide and aminophylline, but no more digitalis or Diuril. Following this procedure and for the four months during which the patient was observed, there was definite improvement in the patient's symptoms. He had only occasional asthma, noticeable when the weather changed or when he ate to excess. The patient then returned to southern Florida where his condition had always been noticeably better. Three months later he died suddenly of "cerebral apoplexy."

This case report is an excellent illustration of a patient with definite organic hypertensive cardiovascular disease whose asthma at first was regarded and treated as cardiac in origin by his attending physician without an effort being made to determine the possibility of its being bronchial in origin. Because it so happened that he was seen by one who was aware of the basic underlying bronchial nature of his asthma, a true differentiation was made and proper treatment instituted. If this had not occurred, the underlying basic allergic asthma might easily have been missed and the patient would have continued to be regarded, as was Case 1 as a case of cardiac asthma. The fact that he died of a cerebral vascular accident and not from cardiac failure is additional proof that the asthma was of bronchial and not cardiac origin and had nothing to do with his death.

It must be admitted that when one sees patients like Cases 1 and 2 who have serious organic heart disease and suddenly begin to have attacks of wheezing dyspnea resembling asthma, perhaps, also, with such signs of early cardiac insufficiency as ankle edema, it is tempting to regard the cardiac condition as basically responsible for the asthma. That the patient should be treated primarily or solely as a cardiac patient without regard for the bronchial element might be excusable under such circumstances. But judging from our experience, few patients present the typical clinical picture presented by these two patients. This makes differential diagnosis even more difficult and perhaps explains why they usually are treated for "cardiac asthma."

A more common clinical error, at least judging from the review of our patients, is to assume that because a patient has asthma and at the same time has either slight or sometimes no evidence of co-existent cardiovascular disease (even hypertension) the asthma is of cardiac origin. This is illustrated in the following case report.

CASE 3.—K. M., female, sixty years of age, was first seen Dec. 5, 1957, with a history of asthma of one year's duration and lower sternal pain of several years' duration, intermittent in character, and not associated with the asthmatic attacks. She had received treatment with digitalis on the assumption that both the pain and asthma were cardiac in nature.

Family history was negative for allergy.

The blood pressure averaged between 130/80 and 150/80 mm. Hg. There was no cardiac abnormalities or evidence of failure. The heart was normal in size. The electrocardiogram was normal. Positive intracutaneous skin tests were obtained to house dust, feathers, timothy, and plantain.

The patient was given iodides and ephedrine but, because of intolerance to ephedrine, steroids in small doses had to be given. Following this therapy there was definite improvement in the symptoms with no further asthma or chest pain. Pollen desensitization was attempted but then discontinued because of reaction, even to small doses. Because of a subsequent recurrence of the lower sternal pain without associated asthma, the patient was readmitted to the hospital for further studies which showed that the pain was of gastric origin, attributed to a chronic gastritis.

In Case 3, the presence of both precordial pain and wheezing dyspnea prompted the attending physician to regard the asthma as being of cardiac origin and to treat the patient upon this basis for a considerable period of time, even though there was no substantiation of the cardiac basis from subsequent cardiological examination.

The satisfactory response of the patient's asthma to the same form of treatment usually instituted for bronchial asthma emphasized the underlying bronchial basis for this patient's complaint (Case 3).

CASE 4.—W. D., male, sixty-five years of age, was first seen in the fall of 1956, with a history of recurrent attacks of typical allergic bronchial asthma for twenty years. Asthma was perennial but seemed worse in the spring as well as from contact with house dust or from dampness or after upper respiratory infections. There was a history of a duodenal ulcer many years before. The patient stated that he had been admitted to another hospital three years previously for severe chest pain which was diagnosed as myocardial infarct. At that time he was given digitalis which he had continued to take until the present time, but with no effect upon the asthma.

Physical examination showed the following symptoms: There were typical asthmatic wheezes throughout the chest, which was emphysematous. The heart was of normal size, the heart sounds were distant because of the pulmonary emphysema; no murmurs were audible. The blood count was normal. The electrocardiogram showed a right bundle branch block. Chest x-ray study showed no abnormalities. Positive intracutaneous skin tests were obtained to house dust, feathers, wool, and to birch and oak tree pollens.

Following the completion of the allergy studies, digitalis was discontinued; he was then given allergy treatment which included house dust desensitization and symptomatic treatment with ephedrine with striking improvement in his asthma.

In Case 4, despite a history of typical allergic asthma of twenty years' duration, the patient was given digitalis for a period of three years probably because of the history of myocardial infarction and abnormal electrocardiogram findings, with no effect upon the asthma. The striking improvement which followed the institution of allergy treatment in this patient is especially noteworthy.

In the following case report, illustrative of others in our series, a different problem in relation to cardiac asthma arose.

CASE 5.—G. L., female, aged sixty-three, was first seen March 10, 1949, with a history of asthma of four to six years' duration and of nasal polyposis. Family history was positive for allergy. Intracutaneous skin tests showed positive reactions to house dust, feathers, tobacco, corn meal, chicken, chocolate, and green pea.

In January, 1950, the patient developed pain in the lower sternal or precordial region unassociated with dyspnea or asthma. For this she consulted her family physician who suggested that both the pain and the asthma might be of cardiac origin. She then consulted a cardiologist who upon repeated examinations failed to find any abnormalities in the cardiovascular system except for an occasional extrasystole. The blood pressure varied between

120/80 to 160/80 mm. Hg but there was no persistent hypertension. The heart was of normal size with no evidence of cardiac failure. X-ray examination showed a slightly prominent aortic arch but was otherwise normal. Further observation showed the precordial pain to be of gastric origin, being relieved by antacids and antispasmotics.

The patient's asthma responded to the administration of bronchodilators, iodides and, when necessary, short courses of Aristocort. Despite her good response to allergy treatment and the assurance by the cardiologist of the absence of heart disease, the patient was not convinced that the asthma was not of cardiac origin. Upon the slightest recurrence of the precordial pain she insisted on returning to the cardiologist for examination which, as always, was normal. Her fear that it was cardiac undoubtedly was enhanced by the fact that her husband had died of myocardial infarction.

This patient is one with definite evidence of an allergic bronchial asthma of more than ten years' duration in whom a possible cardiac basis for the asthma was suggested because of associated lower substernal pain and fleeting mild hypertension. However, repeated complete examinations by a competent cardiologist failed to show any evidence of organic cardiac disease.

It should be remembered that chest pains varying in locations and in intensity are not infrequent in patients with recurrent or chronic asthma. When these pains are localized to the precordial region or to the left axillary area and are associated with wheezing dyspnea or actual asthma and mild hypertension, the attending physician might assume that both the pain and the asthma are of cardiac origin until special and complete examination excludes organic heart disease as a cause. It is important in such instances to remember that such pain can be present in asthmatic patients without implicating cardiac disease as its cause.

As suggested in the previous case reports, the most important disadvantage resulting from a mistaken interpretation of the basic condition responsible for the patient's asthma is the difference in the kind of treatment instituted. Thus, if the asthma has a bronchial origin but is considered and treated primarily as cardiac, little or no benefit will be derived (as in Cases 3, 4, and 5) until allergy treatment is substituted for the cardiac form. But in patients with definite cardiac disease and an associated bronchial asthma, who have been treated only from a cardiac standpoint, a good therapeutic response will not be obtained until additional therapy (either symptomatic or specific) is directed toward the bronchial element of the asthma. This was strikingly illustrated in the following cases.

CASE 6.—M. S., female, seventy-seven years of age, was first seen on Dec. 22, 1958, with a history of asthma of five years' duration, worse in the spring and fall, and associated with marked weight loss. There was a negative family history of allergy. The patient was a known hypertensive of at least fifteen years' duration; her blood pressure ranged from 150/90 to 222/117 mm. Hg, although recently it was within normal limits. There was moderate cardiac enlargement to the left but no heart murmur. Electrocardiographic findings showed left axis deviation and left ventricular hypertrophy. The patient was treated by bed rest, digitalis, and diuretics but showed little benefit from it. But, after the institution of allergy treatment, which included the use of bronchodilators, steroids, and pollen desensitization, there was dramatic improvement, including loss of exertional dyspnea and an eighteen-pound weight gain. The patient had previously looked cachetic as though she had a malignancy.

Case 6 dramatically illustrated the importance of combined cardiac and allergy treatment and the recognition that even a patient of 77 years may have two diseases—namely hypertensive heart disease with mild to moderate congestive failure and coexistent allergic asthma.

Case 7.—M. D., female, aged sixty-eight, was first seen May 13, 1957, because of a wheezing type of dyspnea of one to two years' duration and because of an attack of precordial pain interpreted about a year before as a possible, though questionable, attack of coronary infarction, the diagnosis having been based on the symptoms rather than on electrocardiographic evidence.

Examination showed mild cardiac enlargement, but there was no murmur and no evidence of cardiac failure. The blood pressure was normal. Evidence of mild hypothyroidism was present. The electrocardiogram showed no evidence of infarction, either recent or old. Both the circulation time (Decholin, 15 sec.) and venous pressure (6 mm.) were within normal limits. Intracutaneous skin tests were positive to house dust, timothy, ragweed, and a few clinically unimportant foods.

Prior to admission to the hospital and because of the history of supposed infarction, the patient had been given digitalis and diuretics for a number of months without any improvement of the asthma. Following admission to the hospital she was given bronchodilators, iodides, and steroids. For the first time she showed definite and continued improvement in her asthma until she returned to her own home where the asthma recurred, attributed partially to exposure to house dust and also to changeable weather conditions. She was again given symptomatic treatment with subsequent improvement. Desensitization with extracts of dust and pollens then was begun.

It is to be noted in this patient that she was unsuccessfully treated for heart disease, and it was only after the institution of allergy care that noticeable improvement followed. This emphasizes the necessity of determining whether the asthma in such patients is bronchial in origin and not cardiac.

Finally, although as indicated, errors in omission are made in designating as "cardiac asthmatics" those cardiac patients who have a basic bronchial asthma as the cause of their complaints, it must be remembered that in patients with chronic long-standing true bronchial asthma, accompanied by complicating emphysema and perhaps cor pulmonale, signs of cardiac insufficiency may develop later. However, most of these patients develop signs of right-sided failure with subsequent pulmonary congestion. As a result, the wheezing respirations not infrequently seem to disappear rather than accentuate and to reappear when compensation is fully restored, as in the following case.

Case 8.—M. H., female, thirty-two years of age, was first seen Feb. 4, 1932, in the Outpatient Allergy Clinic with a history of recurrent attacks of typical asthma for eighteen years. Attacks were nocturnal in character, lasting formerly two to three days, and were relieved by bronchodilators including epinephrine. More recently the patient noted that the attacks were milder and less acute; however, she also had attacks of palpitation, dyspnea, and increasing swelling of the legs. The patient gave a history of severe acute rheumatic fever late in childhood, for which she was bedridden for a long time, which resulted in secondary cardiac damage. The patient was admitted to the hospital because of cardiac decompensation. Physical examination at that time showed the following symptoms: Numerous crepitant and subcrepitant râles were present throughout the lungs but no wheezing respiration was detectable. Dullness upon percussion was noted over both upper lobes. The heart was markedly enlarged to the left and a harsh systolic murmur was heard. Heart

sounds were very irregular. The electrocardiogram showed auricular fibrillation. Differential blood counts showed eosinophils, 3 to 6 per cent. Positive intracutaneous skin test reactions were obtained to house dust, ragweed, and some clinically unimportant foods. X-ray study of the chest showed tremendous enlargement of the heart, with a volume at least four times normal. The shape was characteristic of mitral regurgitation with tremendous enlargement of the left auricle as well as the left ventricle. Chronic passive congestion of the lung vessels was noted.

When the patient was first seen in the Outpatient Clinic, the asthmatic wheezing was definite and pronounced. But with the onset of insufficiency, the wheezing became milder and then absent. Because of repeated attacks of cardiac decompensation, the patient had to be hospitalized repeatedly for cardiac treatment, including digitalization and diuretics. As soon as compensation became restored, the mild asthmatic wheeze again was noticeable. But this did not persist because attacks of decompensation became increasingly frequent until the patient's death, more than a year later. At no time during her hospitalization for cardiac insufficiency was there any evidence of asthmatic breathing or wheezing respiration.

Case 8 illustrates the coexistence of allergic bronchial asthma and the cardiac dyspnea of rheumatic heart disease. It is interesting to note that when the cardiac picture was predominant, it overshadowed completely the asthmatic paroxysms.

A similar situation was present in the following case.

CASE 9.—N. S., female, aged forty-five, was first seen in the Outpatient Allergy Clinic in 1950. There was a history of recurrent attacks of bronchial asthma for thirteen years, aggravated by contact with house dust or cat hair and also by ingestion of fish, clams, strawberries, and bananas. The patient had had asthma during childhood between the ages of 5 and 12 years. The family history was positive for allergy. The patient received allergy treatment with some improvement in her symptoms. Ankle edema was noted for the first time during the past six months.

She was next seen in 1957 during the first of her many subsequent hospital admissions because of heart failure. There were many signs of right-sided congestive failure—large liver, ankle edema, dyspnea, increased circulation time (Decholin, 37 sec.; ether, 13 sec.), increased venous pressure (26 mm.), and electrocardiographic changes suggesting possible atrial and ventricular disease and coronary artery disease. It was noteworthy that during her admission in January, 1957, and during subsequent ones, because of right-sided heart failure, the patient had no acute attacks of asthma and no wheezing respiration was detected on examination of the chest.

As in Case 8, the disappearance of the asthmatic wheezing during periods of right-sided heart failure was especially noteworthy in Case 9. These situations, however, usually present no problem in diagnosis, since the asthma, previously present, disappears and is replaced by signs of insufficiency. But, such patients differ from those discussed earlier who have hypertensive organic heart disease and who subsequently develop insufficiency with acute left-sided failure and ensuing pulmonary edema. If the patient already has bronchial asthma as a coexistent disease or has an asthmogenic tendency, then the sudden shock of acute failure may bring on either an acute attack of asthma or wheezing respiration, as in the following case.

CASE 10.—W. V., male, aged fifty-two, was first seen October, 1956, with a history of recurrent attacks of asthma for ten years, preceded by perennial allergic rhinitis of about twenty-five years' duration. His father had had "miner's asthma." The patient also had a

history of three attacks of myocardial infarction since 1952, each accompanied by signs of congestive failure and ankle edema. Excessive ingestion of salt caused increased swelling of ankles and weight gain as well as some dyspnea but very little wheezing, whereas exposure to house dust or upper respiratory infection induced asthma.

Physical examination showed moderate emphysema, expiratory wheezes were heard throughout the chest, and some ankle edema was present. A chest roentgenogram showed emphysematous bullae present in both upper lobes. The electrocardiogram was compatible with pulmonary emphysema with prominent peaked P wave in 2 and 3 aV_F. There were signs of old anterolateral myocardial infarction. Circulation times were prolonged (Decholin, 21 sec.; ether time, 15 sec.). Positive intracutaneous skin tests were obtained only to house dust.

The patient was treated from a cardiac standpoint with digitalis and diuretics but with little effect on the asthma. Following the institution of allergy treatment, including bronchodilator drugs, such as Isuprel and ephedrine, and house dust desensitization there was noticeable improvement in his asthma.

The striking feature of Case 10 was the coexistence in the same patient of allergic asthma and organic heart disease with left-sided failure. It is noteworthy that the asthma was made worse not only with onset of cardiac failure but also after dust contact, and he did not improve until he was treated for both conditions.

As already indicated, the second or control group consisted of 109 unselected patients whose hospital records were reviewed at random for evidence of asthma, either as definite acute attacks or as wheezing respiration recorded in the history or present upon physical examination. Most of these patients had hypertensive cardiac or coronary artery disease with insufficiency; only a small percentage (10 per cent) had rheumatic heart disease. We found only one patient in this control group, including those with pulmonary edema resulting from failure, in whom wheezing respiration had been detected, but no further data were recorded as to its basis or as to the presence of other allergic symptoms. One must conclude therefore that, in a control group of cardiac patients who had no associated allergic asthma, organic heart disease, even with acute failure, does not of itself induce wheezing respiration or signs of asthma unless the individual is specifically predisposed or has an underlying asthmatic condition.

DISCUSSION

As stated at the outset, it seemed to us that if "cardiac asthma" is a distinct entity which occurs especially in hypertensive cardiovascular patients, then one should find evidence in patients with organic heart disease to explain the occurrence of their asthma. However, in our study of the 103 patients with coexistent bronchial and cardiac disease, we have shown that asthma, either as an acute attack or in the form of wheezing dyspnea, occurred primarily because of either a coexistent asthma or an underlying asthmogenic tendency and not because of the existing cardiac disease. This was especially evident in patients with the combined diseases whose asthma improved only after appropriate measures were instituted against the bronchial (including the allergy) factor of the disease.

Furthermore, in a control investigation of 109 patients with organic cardiovascular disease and no asthma, no evidence was found that the existence of the cardiac disease without or even with failure would induce wheezing respiration in the absence of coexistent asthma or an asthmogenic tendency. This confirms an old observation by Rackemann[10] in 1931 who wrote that "if cardiac asthma depended upon simple heart failure with pulmonary stasis, one would suppose that at least a large portion of patients with heart disease would show asthma but they do not."

The evidence obtained in a review of these two groups clearly indicates that in patients presumed to have cardiac asthma there actually is a coexistence of two diseases, one cardiac and the other bronchial. In some patients these may exist independently at all times and exert no special influence on one another. In others, especially as the result of acute left ventricular failure and consequent pulmonary edema, the patient may show wheezing respiration or an actual attack of asthma which is provoked in the same manner as might be induced by other nonspecific precipitating factors, such as exposure to cold wind or to strong irritating odors. In such instances, the asthma is bronchial not cardiac in origin, even though the precipitating factor in some patients may be of cardiac origin. It would not seem justified, therefore, to label the asthma in the cardiac patients as "cardiac" any more than we would speak of the other forms as "cold wind asthma," "tobacco asthma," etc. To continue to label these patients as having "cardiac asthma" is to revert to the early days of this century when asthma was designated as bronchial, cardiac, renal, thymic, reflex, etc. Since we have eliminated these earlier designations and now consider all asthma as bronchial, it would seem appropriate and proper to likewise eliminate the designation "cardiac" so as to lessen the confusion in terminology. What is even more important, however, is that the recognition of the underlying bronchial basis of the asthma would lead to institution of proper treatment directed against the bronchial as well as the cardiac aspects, and eventually lead to better clinical and therapeutic results.

SUMMARY AND CONCLUSIONS

Clinical investigation of 103 patients with asthma and coexistent cardiovascular disease, some of whom had been designated as having and were treated for "cardiac asthma," showed that cardiac disease is not the basic cause of asthma and that typical so-called "cardiac asthma" is rare. The term actually is a misnomer and might profitably be abandoned. Coexistence of asthma with heart disease is not uncommon; and the latter even occasionally may be important in the production of wheezing respiration in an asthmatic patient, especially as a result of insufficiency. But the basic bronchial cause of the asthma should be recognized clinically, since asthmatic patients, treated solely for their coexistent cardiac disease and refractory to such treatment, improve when additional and proper allergy treatment is given.

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A COMPARISON OF THE GROWTH SUPPRESSIVE EFFECT OF CORTISONE, PREDNISONE, AND OTHER ADRENAL CORTICAL HORMONES

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THERE is considerable reported evidence indicating that adrenal cortical hormones of the cortisone type can suppress linear growth. Children with Cushing's syndrome due to hypersecretion of these hormones grow more slowly than normal children.[1] Experimental animals, given sufficient amounts of cortisone or ACTH, grow at a reduced rate.[2-4] When children are treated for prolonged periods with enough cortisone,[5-6] prednisone,[7] or methylprednisolone,[7] there is evidence of linear growth retardation which may be reversed by discontinuing therapy or by reducing dosage below a critical growth suppressive level.

There are data which suggest that adrenal corticosteroids may differ in their potency as growth inhibitors. The critical growth suppressive dosage of cortisone has been reported to be 45 mg. per square meter of body surface per day[5]—that of prednisone 5.1 mg. per square meter of body surface per day.[7] These two figures were derived in different groups of patients by different observers and it is therefore hazardous to compare them. However, since cortisone is generally considered to be about one fifth as potent as prednisone as a therapeutic agent in allergic disease,[8, 9, 10] any indication that it may be only one ninth as potent as prednisone as a growth suppressive agent should be confirmed or disproved.

This present study was initiated to compare the growth inhibiting effect of prolonged treatment with cortisone, prednisone, methylprednisolone, triamcinolone, and fluprednisolone† in children with severe, persistent, chronic bronchial asthma.

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†Cortisone was supplied as Cortone Acetate by Merck Sharp & Dohme, West Point, Pa., and as Cortisone Acetate by The Upjohn Company, Kalamazoo, Mich. Prednisone (Deltasone), methylprednisolone (Medrol), and fluprednisolone (6-fluoro prednisolone, Alphadrol) were supplied by The Upjohn Company. Triamcinolone was supplied as Aristocort by Lederle Laboratories, Pearl River, N. Y.

MATERIALS AND METHODS

Since January, 1955, in the Pediatric Allergy Clinic of The Johns Hopkins Hospital, observations have been made of the growth of nineteen children with intractable perennial asthma who have received cortisone, prednisone, methylprednisolone, triamcinolone, or fluprednisolone alone or in sequence more or less continuously for six months or longer. Table I shows the age, race, and sex of each patient, the duration of observation before, during, and after corticosteroid therapy, and the average dosages employed. Steroid dosage is expressed in milligrams per square meter of body surface per day in order to facilitate comparison of dosages employed in patients of different size.[5] Average daily dosage was calculated by dividing the total amount of drug given during a given period by the number of days in the period.

Height and weight were measured with the patients in the standing position and recorded on Stuart anthropometric charts* (Fig. 1).[5] Since 1957, these measurements have been made at close intervals (usually every one or two weeks) to minimize error. With these charts, observed and normal increase in weight and height during any observation period could be determined and compared. The linear growth rate in per cent of normal during a given period of observation was calculated by dividing the observed increase in height by the expected normal increase in height and multiplying by 100. The weight gain in per cent of normal during a given period of observation was calculated by dividing the observed increase in weight by the expected normal increase in weight and multiplying by 100.

Patients receiving cortisone were maintained on a low salt diet and potassium chloride,† 0.3 Gm. three times each day. Some patients receiving prednisone were given a similiar dosage of potassium chloride as indicated in Table I.

In every case, effort was made to use the least amount of corticosteroid that would suffice to control asthma. To facilitate reduction in steroid dosage, indicated supplementary therapy was continued during the course of steroid therapy including some or all of the following: allergen avoidance, desensitization, bronchodilators, expectorants, and antibiotics.

RESULTS

Linear Growth.—The data are shown in Table I and Fig. 2.

Before onset of corticosteroid therapy, linear growth rate was essentially normal.

During therapy with prednisone or methylprednisolone, growth retardation was evident when the average dosage for a six month or longer period of observation exceeded 5.0 mg. per square meter of body surface per day, and growth was normal when the average dosage was less. The degree of growth

*Stuart anthropometric charts were supplied by Mead Johnson & Co., Evansville, Ind.

†Potassium chloride was supplied as Potassium Chloride Enseals by Eli Lilly and Co., Indianapolis, Ind.

retardation was roughly proportional to steroid dosage and appeared similar with either prednisone or methylprednisolone.

During therapy with triamcinolone and fluprednisolone, growth retardation was likewise evident.

During cortisone therapy, using dosages equivalent in predictable anti-inflammatory effect to those employed with the other steroids and securing equally good control of asthma, linear growth was normal or accelerated.

After cessation of corticosteroid therapy, linear growth rate was usually accelerated.

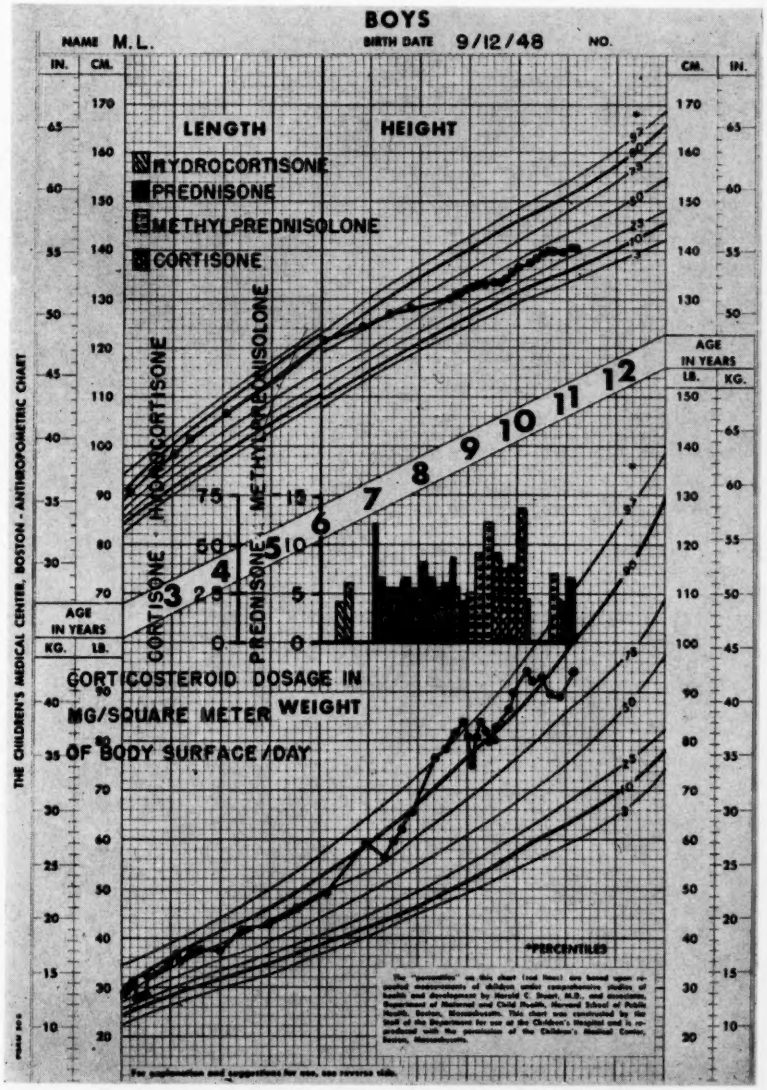

Fig. 1.—Patient M. L. Height and weight measurements and average daily corticosteroid dosage have been plotted on a Stuart anthropometric chart.

TABLE I. SUMMARY OF DATA ON NINETEEN PATIENTS WITH CHRONIC ASTHMA WHO RECEIVED CORTICOSTEROID THERAPY FOR SIX MONTHS OR LONGER

PATIENT	RACE	SEX	AGE AT ONSET OF ASTHMA (YEARS)	DURATION OF OBSERVATION PERIOD (MONTHS)	AGE DURING OBSERVATION PERIOD (YEARS)	CORTICOSTEROID GIVEN DURING OBSERVATION PERIOD	AVG. DAILY CORTICOSTEROID DOSE IN MG./SQ. M. BSA/ DAY DURING OBSERVATION PERIOD	LINEAR GROWTH RATE (% OF NORMAL)	WEIGHT GAIN (% OF NORMAL)
J. M.	N	M	1.3	2	1.5 - 1.7	None	0	100	100
				2	1.8 - 2.0	Hydrocortisone	36	0	ND
				22	2.0 - 3.8	Prednisone	12.9 (2)*	0	45
				1	3.8 - 3.9	Prednisone	8.5)	75	100
				3	3.9 - 4.2	Methylprednisolone	8.5 (		
				7	4.2 - 5.2	Cortisone†	57.0 (1)*	140	200
H. W.	N	M	0.5	20	2.5 - 4.2	Prednisone	7.5 (2)	75	67
J. R.	W	M	1.2	6	2.1 - 2.7	None	0	100	67
				11	2.7 - 3.6	Triamcinolone	5 (5)*	41	80
M. S.	N	M	0.2	17	1.75- 3.3	None	0	100	100
				4	3.3 - 3.7	Prednisone	9.7	50	200
				2	3.7 - 3.8	None	0	100	0
				1	3.8 - 3.9	Methylprednisolone	8.2	0	100
				3	3.9 - 4.2	Prednisone	7.0	50	100
				5	4.2 - 4.6	Methylprednisolone	6.3	40	100
				11	4.6 - 5.5	Cortisone†	45.0 (1)	133	300
D. A.	W	F	1.4	12	4.0 - 5.0	Prednisone	7.4 (2)	57	100
				6	5.0 - 5.5	Methylprednisolone	4.4 (3)*	100	–133
				11	5.7 - 6.6	Cortisone†	38.0 (1)	100	180
				2	6.6 - 6.7	None	0		
				1	6.7 - 6.8	Prednisone†	6		
				6	6.8 - 7.3	None	0	140	100
D. P.	W	M	0.2	10	4.2 - 5.1	Cortisone†	49.0 (1)	100	100
D. S.	N	F	0.9	4	4.6 - 4.9	None	0	100	0
				2	4.9 - 5.1	Methylprednisolone	9.5	0	50
				8	5.1 - 5.7	None	0	166	150
				7	5.7 - 6.3	Cortisone†	30.0 (1)	166	150
				7	6.3 - 6.9	None	0	133	50
S. S.	W	F	3.2	13	3.8 - 4.9	None	0	113	60
				11	4.9 - 5.8	Prednisone	6.4 (2)	60	200
				8	5.8 - 6.0	None	0	125	100
L. G.	N	M	1.3	11	4.2 - 5.1	None	0	83	50
				6	5.1 - 5.6	Methylprednisolone	8.2 (3)	17	250
				5	5.6 - 6.0	None	0	120	100
				6	6.0 - 6.5	Cortisone†	53.0 (1)	114	50
				8	6.5 - 7.1	None	0	150	225
C. M.	W	F	1.2	3	5.8 - 6.1	Hydrocortisone	31.0	69	50
				23	6.1 - 8.0	Prednisone	7.3 (2)	69	50
				7	8.0 - 8.7	Methylprednisolone	4.6 (3)	100	150
				9	8.7 - 9.4	Cortisone†	28.0 (1)	125	175
				7	9.4 -10.0	None	0	167	50
D. L.	N	M	2.0	24	3.6 - 5.9	None	0	100	129

C. M.	W	F	1.2	3	5.8 - 6.1	Hydrocortisone	31.0	69	50
				23	6.1 - 8.0	Prednisone	7.3 (2)	69	50
				7	8.0 - 8.7	Methylprednisolone	4.6 (3)	100	150
				9	8.7 - 9.4	Cortisone†	28.0 (1)	125	175
				7	9.4 -10.0	None	0	167	50
D. L.	N	M	2.0	24	3.6 - 5.9	None	0	100	129
				9	5.9 - 6.5	Prednisone	7.6 (2)	33	100
				7	6.5 - 7.1	Methylprednisolone	7.1 (3)	29	100
				4	7.1 - 7.5	None	0	200	135
				4	7.5 - 8.0	Cortisone†	24.0	167	200
				2	8.0 - 8.3	None	0	110	100
				6	8.3 - 8.8	Fluprednisolone	2.0 (4)*	33	33
M. L.	N	M	0.8	52	2.0 - 6.3	None	0	100	100
				4	6.3 - 6.7	Hydrocortisone	27.0	ND	400
				5	6.7 - 7.1	None	0	ND	100
				22	7.1 - 8.8	Prednisone	7.1 (2)	40	170
				1	8.8 - 8.9	Methylprednisolone	5.5	100	–400
				2	8.9 - 9.0	Prednisolone	4.0		
				6	9.0 - 9.5	Methylprednisolone	8.7	50	300
				9	9.5 -10.2	Cortisone†	43.0 (1)	100	138
				5	10.2 -10.7	None	0	100	–25
				3	10.7 -10.9	Methylprednisolone	6	0	0
				3	10.9 -11.2	Prednisone†	5.2	50	150
R. E.	N	M	0.3	11	6.6 - 7.6	Cortisone†	46.0 (1)	100	100
				7	7.6 - 8.2	Prednisone†	7.1 (2)	57	133
C. J.	N	M	6.8	4	7.2 - 7.5	Prednisone	11.0	0	100
				8	7.5 - 8.2	Methylprednisolone	8.4 (3)	30	117
				11	8.2 - 9.2	Cortisone†	45.0 (1)	150	200
				2	9.2 - 9.4	None	0	100	13
				7	9.4 - 9.9	Prednisone†	12.9 (2)	17	–33
T. D.	W	M	4.0	9	8.3 - 9.0	Prednisone	5.7 (2)	50	110
				4	9.0 - 9.3	Methylprednisolone	4.5	25	0
				6	9.3 - 9.8	None	0	133	133
				8	9.8 -10.5	Cortisone†	35.0 (1)	116	100
				4	10.5 -10.7	None	0	100	133
				6	10.7 -11.3	Fluprednisolone	1.9 (4)	50	25
E. R.	W	F	1.5	17	9.3 -11.0	Prednisone	5 (2)	100	386
R. G.	N	M	9.0	14	9.6 -10.8	Prednisone	5.1 (2)	50	72
				6	10.8 -11.2	Methylprednisolone	4.4 (3)	100	143
				3	11.2 -11.5	None	0	260	100
				8	11.5 -12.2	Cortisone†	31.0 (1)	160	140
				3	12.2 -12.4	None	0	100	75
				1	12.4 -12.5	Methylprednisolone	4.5	25	0
				6	12.5 -13.0	Prednisone†	5.0	37.5	60
D. G.	N	M	7.8	25	7.6 - 9.9	None	0	100	40
				23	9.9 -11.8	Prednisone	5.4 (2)	55	189
				6	11.8 -12.3	Methylprednisolone	4.25 (3)	110	150
				8	12.3 -13.0	None	0	238	100
W. S.	W	M	0.8	6	11.2 -11.8	Methylprednisolone	5.4 (3)	66	–60
				10	11.8 -12.6	Cortisone†	18.0 (1)	140	56

*(1-5) These doses of corticosteroid given during an observation period of six months, or longer, and averaged in Table II. (1) Cortisone; (2) prednisone; (3) methylprednisolone; (4) fluprednisolone; (5) triamcinolone.

†These patients received potassium chloride, 0.3 Gm. three times each day, in addition to corticosteroid.

Potassium chloride administration did not affect linear growth (Table I).

Weight Gain.—These data are shown in Table I and Fig. 3. Before onset of corticosteroid therapy, weight gain was more often subnormal than normal. During corticosteroid therapy, weight gain was usually normal or accelerated, even when linear growth rate was retarded, and no significant difference was noted between the various corticosteroids in this regard. After cessation of corticosteroid therapy, weight gain tended to be normal.

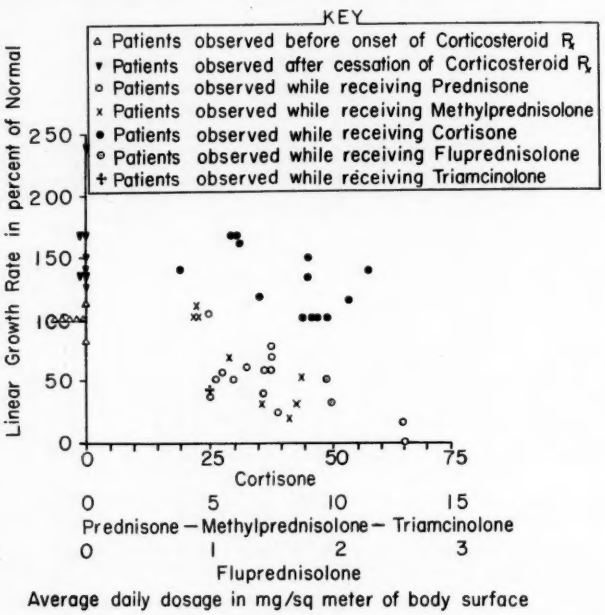

Fig. 2.—Relationship between average daily corticosteroid dosage and linear growth rate in the nineteen patients presented in Table I. Each plotted point represents data from at least six consecutive months of observation.

Minimum Effective Dose of Corticosteroid.—All of the corticosteroids employed seemed to be equally effective in controlling asthma, when given in adequate quantity. The required amount of any one of these agents varied widely and usually increased during periods of excessive exposure to causative antigen, infection, and psychic stress. Effort was made to give no more than the required amount and it is believed that within human error the minimum effective dose was employed. The average daily dose of each corticosteroid given to each patient is shown in Table I. Table II shows the average value and range for each corticosteroid of those daily doses listed in Table I that were determined during at least six months of observation.* The ratio between these average minimal daily effective doses gives an indication of the relative potency of these agents as therapeutic agents for asthma in these patients. Cortisone was 7.5/40 or about one fifth as potent as prednisone and 6.2/40 or about one sixth as potent as methylprednisolone. The number of patients treated with

*Markers point out the doses listed in Table I that were averaged to produce the figures given in Table II.

fluprednisolone and triamcinolone is too small to justify similar calculations with reference to their relative potency.

CASE REPORTS

CASE 1.—Patient M. L. Severe perennial asthma began at the age of 9 months and was intractable despite intensive therapy, including avoidance of allergens, desensitization, psychotherapy, bronchodilators, expectorants, and antibiotics. However, linear growth (Fig. 1) proceeded along the 75th percentile at 100 per cent of the normal rate until corticosteroid therapy was begun. Between the ages of 7 years 1 month and 9 years 6 months, the patient received prednisone, prednisolone, and methylprednisolone, alone or in combination, in an

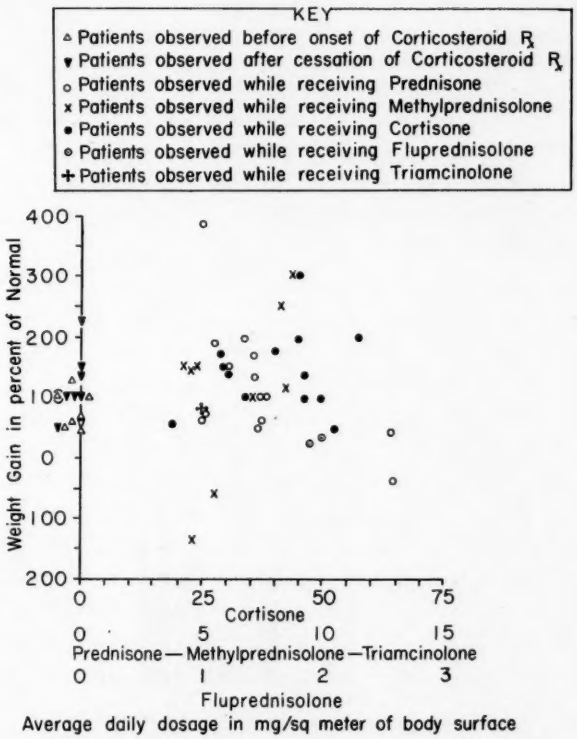

Fig. 3.—Relationship between average daily corticosteroid dosage and weight gain in the nineteen patients presented in Table I. Each plotted point represents data from at least six consecutive months of observation.

TABLE II*

	NUMBER PATIENTS TREATED FOR SIX MONTHS OR LONGER	AVERAGE DAILY DOSE IN MG./SQ. METER BSA	
		AVERAGE	RANGE
Cortisone	13	40	18-57
Prednisone	13	7.5	5-12.9
Methylprednisolone	9	6.2	4.3-8.7
Fluprednisolone	2	2.0	1.9-2.0
Triamcinolone	1	5.0	

*A comparison of the average daily doses of cortisone, prednisone, methylprednisolone, fluprednisolone, and triamcinolone given to the nineteen children with bronchial asthma presented in Table I. Each dose was determined during 6 months or more of observation and represents the total dosage given during the observation period divided by the number of days in the observation period.

average dosage of 7 mg. per square meter of body surface per day (7.4 mg. per day). Concomitantly, despite improvement of asthma and accelerated weight gain, linear growth occurred at 47 per cent of the previously normal rate. Between the ages of 9 years 6 months and 10 years 3 months, the patient received cortisone in an average dosage of 43 mg. per square meter of body surface per day, and growth rate accelerated to 100 per cent of the normal rate. When corticosteroid therapy was stopped between the ages of 10 years 3 months and 10 years 8 months, linear growth continued at 100 per cent of the normal rate. However, when between the ages of 10 years 8 months and 11 years 2 months, the patient received methylprednisolone and prednisone in an average dosage of 6 mg. per square meter of body surface per day, growth was slowed to 25 per cent of normal.

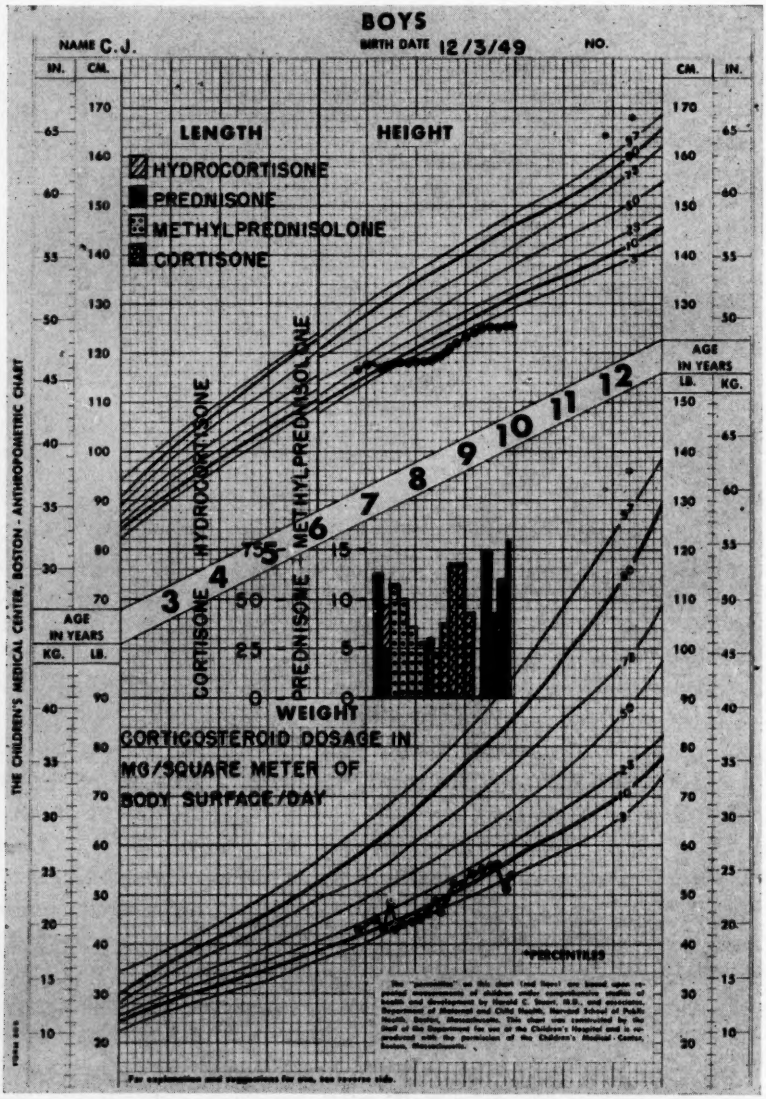

Fig. 4.—Patient C. J. Height and weight measurements and average daily corticosteroid dosage have been plotted on a Stuart anthropometric chart.

Cortisone dosage employed here was entirely comparable with regard to predictable anti-inflammatory effect to that of prednisone and methylprednisolone and produced similar suppression of asthma. Notwithstanding, growth was normal during the period of cortisone therapy, and retarded during the periods of therapy with prednisone and methylprednisolone which preceded and followed cortisone.

CASE 2.—Patient C. J. Severe perennial asthma began at the age of 6 years 10 months and continued despite extensive therapy including avoidance of allergens, desensitization, bronchodilators, and antibiotics. Between the ages of 7 years 2 months and 8 years 3 months, he received prednisone and methylprednisolone in an average daily dosage of 9.3 mg. per square meter of body surface. Concomitantly, despite improvement in asthma and normal weight gain, linear growth occurred at only 17 per cent of the expected normal rate. Between the ages of 8 years 3 months and 9 years 2 months, he received cortisone in an average daily dosage of 45 mg. per square meter of body surface. Concomitantly, although control of the asthma was equally good, linear growth accelerated to 150 per cent of the normal rate. Between ages 9 years 4 months and 9 years 11 months, the patient was returned to prednisone therapy in an average daily dosage of 12.9 mg. per square meter per day and linear growth rate again slowed to 17 per cent of normal.

DISCUSSION

The linear growth retardation observed in asthmatic children receiving prednisone, methylprednisolone, triamcinolone, and fluprednisolone can be logically attributed to steroid therapy. It appeared at the time of onset of such therapy. The degree of inhibition was roughly proportional to the average dosage employed. Cessation of therapy or reduction in dosage below the critical level of growth suppression was followed by the appearance of a normal or accelerated growth rate. While chronic asthma and inanition have been reported to be associated with growth suppression,[11, 12] there is little evidence that these factors were responsible for growth suppression in the corticosteroid-treated children described here. In general, before corticosteroid therapy, asthma was severe and growth was normal; whereas, during therapy, asthma and nutrition were improved and growth was retarded as long as sufficient steroid was given. Observations on the growth of fifty-two children in this clinic with asthma sufficiently mild to require no steroid therapy indicated essentially normal growth.[7]

Evidence derived from studies of experimental animals has indicated that adrenal cortical hormones suppress linear growth through inhibition of epiphyseal cartilage cell proliferation and this effect is antagonistic to the skeletal effect of pituitary growth hormone.[13] A direct inhibiting effect on the growth of fibroblasts in tissue culture has also been shown.[14] This growth suppressive effect "may be attributed to a protein catabolic effect, to inhibition of protein anabolism, or merely to withdrawal of amino acids from the metabolic pool for the purpose of gluconeogenesis."[15] Moon facies has been observed frequently in children with growth suppression associated with corticosteroid therapy.[5, 7]

It is noteworthy that linear growth retardation was not observed in any asthmatic child receiving cortisone, but was the rule in those receiving prednisone, methylprednisolone, triamcinolone, and fluprednisolone. With cortisone, normal growth was obtained even with dosages exceeding 55 mg. per square

meter per day, although it seems probable from other reports that still higher dosages of cortisone would cause growth suppression.[5, 6] With prednisone and methylprednisolone, growth retardation was evident when the average dosage for a period of six months or longer of observation exceeded 5.0 mg. per square meter of body surface per day. Therefore, cortisone was less than one tenth as potent as prednisone and methylprednisolone as a growth inhibiting agent in these patients.

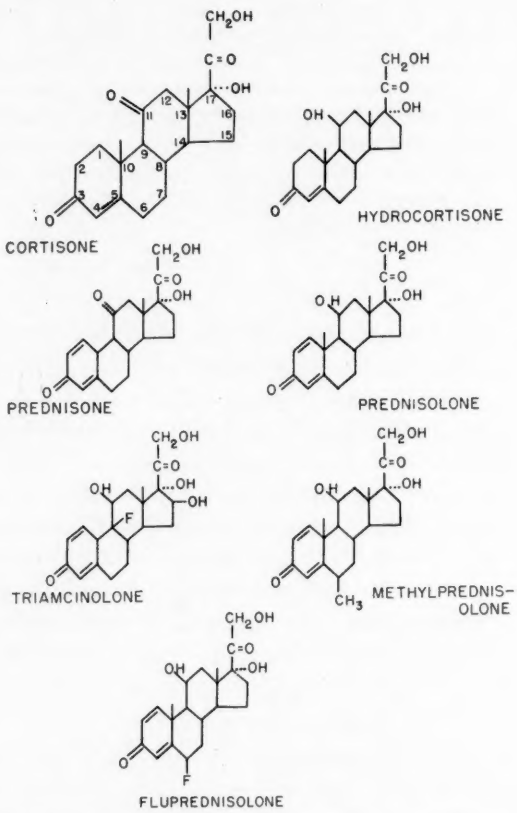

Fig. 5.—Structural formulas of corticosteroids discussed. Prednisone, prednisolone, methylprednisolone, triamcinolone, and fluprednisolone are all characterized by dehydrogenation of the cortisone or hydrocortisone nucleus at positions C_1 and C_2 with introduction of an unsaturated double bond between these two carbon atoms.

Cortisone is usually considered to be about one fifth as potent as prednisone and one sixth as potent as methylprednisolone in the treatment of bronchial asthma.[8-10, 16-18] The average daily dosages of these agents employed in this study were within this range (Table II). Control of asthma in these cases was equally good with all corticosteroids employed.

This study indicates that cortisone is about one fifth to one sixth as potent as prednisone and methylprednisolone as a therapeutic agent in asthma but only one tenth as potent as a growth inhibiting agent. These relationships probably explain the observation that those children who received enough cortisone to

suppress asthma grew normally while those who received enough prednisone, methylprednisolone, triamcinolone, and fluprednisolone to produce a similar suppressive effect on asthma usually grew at a retarded rate.

Hill has emphasized the rarity of growth suppression in eczematous children receiving prolonged cortisone therapy.[19]

It seems evident that the new synthetic steroids (prednisone, methylprednisolone, triamcinolone, and fluprednisolone), while being less active than cortisone with reference to sodium retention and potassium excretion, are more active with regard to linear growth inhibition. The differences between the chemical structures of these various corticosteroids are shown in Fig. 5. It is of interest that all these "new" steroids are characterized by dehydrogenation of the cortisone or hydrocortisone nucleus at positions C_1 and C_2 with introduction of an unsaturated double bond between these two carbon atoms. It seems likely that this structural change may be proved to be responsible for the change in pharmacologic effect.

The demonstration that the effects of corticosteroids on growth and electrolytes are not inseparably linked with their therapeutic (anti-inflammatory) effect in asthma raises the hope that some change in the molecule can be accomplished which will permit maximum therapeutic effect with a minimum of both electrolyte derangement and growth inhibition.

SUMMARY

Normal linear growth was noted in all of thirteen children given sufficient cortisone over a period of six months or longer to suppress asthma. Linear growth suppression was noted in twelve of thirteen children given prednisone, five of nine given methylprednisolone, the two given fluprednisolone, and in the one given triamcinolone, when sufficient corticosteroid was given for a similar period of time to produce the same degree of suppression of asthma.

Evidence is presented indicating that cortisone is about one fifth as potent as prednisone and one sixth as potent as methylprednisolone as a therapeutic agent in asthma, but only one tenth as potent as each as a growth inhibiting agent.

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STUDIES IN EGG WHITE ANTIGEN CONTENT OF INFLUENZA VIRUS VACCINES

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IT IS WELL KNOWN that egg proteins are found in viral and rickettsial vaccines and that the use of such vaccines in egg-sensitive persons may result in allergic reactions. The manifestations which have been reported encompass nearly the entire spectrum of allergic phenomena.[1, 2] The incidence of such reactions following the administration of egg-contaminated vaccines has been reported to be about 0.5 per cent of the general population.[2] A severe constitutional reaction from a test dose (0.02 ml.) with influenza virus vaccine has been reported.[3]

Stull[4] studied the egg protein content of viral and rickettsial vaccines by passive-transfer tests with egg reagin-bearing sera. Single passive-transfer tests were performed by him with each antigenic substance and with each antiserum. Ratner and Untracht[2] were able to show by random direct skin testing that the vaccines prepared by red blood cell elution method contained the greatest amount of egg proteins, and elicited larger skin reactions than vaccines prepared by Sharples centrifugation or by alcohol precipitation. In a recent publication by Cohen and Mines,[5] a marked variation in the egg white and egg yolk components of viral and rickettsial vaccines was demonstrated. These studies were performed with anti-egg rabbit sera in agar diffusion plates by the Ouchterlony technique.

The purposes of the present study are to determine, by means of the passive-transfer method in adequate trials, the amount of egg white antigen which is present in commercially available influenza virus vaccines, and to compare their egg white antigen content. The authors are aware that influenza virus vaccine contains both egg white and egg yolk antigen components. Because of the unavailability of a fully satisfactory egg yolk extract, we have confined our report to egg white as the indicator of egg antigen content of the vaccine.

METHODS AND MATERIALS

Sera obtained from two patients (S and R) which contained reagins to egg were used for the passive-transfer studies. Clinically, egg-containing foods

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caused asthmatic attacks and bouts of diarrhea in Patient S and initiated intense pruritic episodes in Patient R. Direct intracutaneous testing with egg white extract in a concentration of 0.001 mg. N per milliliter caused a marked (4+) skin reaction in both patients. Further indication of the potency of the sera was evidenced by the fact that passively sensitized skin sites flared up after ingestion of egg or fowl by the recipients. Neither serum contained reagins to penicillin.

The egg white extract was prepared by the Allergy Laboratory of The Jewish Hospital of Brooklyn. For study purposes, it was prepared with buffered saline in tenfold dilutions, the testing strengths varying from 1 mg. N per milliliter to 0.0000001 mg. N per milliliter.

The influenza virus vaccines were obtained commercially. Three basic methods are used to concentrate the virus. The red blood cell elution method entails concentration of the virus by adsorption on and elution from red blood cells of chick embryo (brands A and E). By the Sharples centrifugation method, concentration of the virus is accomplished by differential ultracentrifugation (brands B and D). With the protamine sulfate precipitation method, concentration is achieved by precipitation with protamine sulfate and separation by ultracentrifugation (brand C). The vaccines were polyvalent or monovalent and manufactured by Eli Lilly and Co., Parke, Davis and Co., Merck Sharp & Dohme, Lederle Laboratories, and Pitman-Moore Co. For testing purposes the vaccines were prepared in tenfold dilutions with buffered saline up to a dilution of 1:1,000,000.

Eight to eighteen skin sites were prepared on the arms of forty-three nonallergic recipients by the intracutaneous injection of 0.05 ml. of serum. Each recipient was instructed to maintain a diet free of egg and fowl for twenty-four hours prior to preparation of the skin and for the duration of the tests. Sites were tested three to four days after sensitization. When the same recipients were resensitized for another passive-transfer test, the opposite and previously unused arm was prepared after a rest period of one week.

Passive-transfer testing was started with high dilutions of both egg white and influenza virus vaccine. If no reaction was elicited, testing was continued successively with tenfold stronger solutions of the antigens at different sites. About 0.01 ml. of antigen was injected intracutaneously into the passively sensitized sites and into adjacent normal skin as controls. After fifteen minutes, the reactions at the test and control sites were graded according to the size of the wheal and surrounding erythema. The smallest amount of antigenic material which elicited a definite passive-transfer reaction on a sensitized site and a negative control test was considered to be the threshold level of that antigen for the particular recipient. The threshold responses for each test substance were determined on numerous subjects in order to ascertain the reaction pattern of the majority of recipients. Finally, the reaction patterns for egg white and for the five brands of vaccine were compared, and the equivalent content of egg white in the various vaccines estimated.

RESULTS

The threshold reaction for egg white was determined in twenty-eight recipients sensitized with undiluted S serum. An egg white solution containing 0.00001 mg. N per milliliter was found to be the lowest concentration which could elicit a positive passive-transfer reaction in eighteen of the twenty-eight recipients (64 per cent) sensitized with this serum (Fig. 1). Seven recipients (25 per cent) showed a threshold response at the level of 0.0001 mg. N per milliliter, while one recipient each showed threshold responses at 0.0000001 mg. N, 0.000001 mg. N, and 0.001 mg. N per milliliter, respectively.

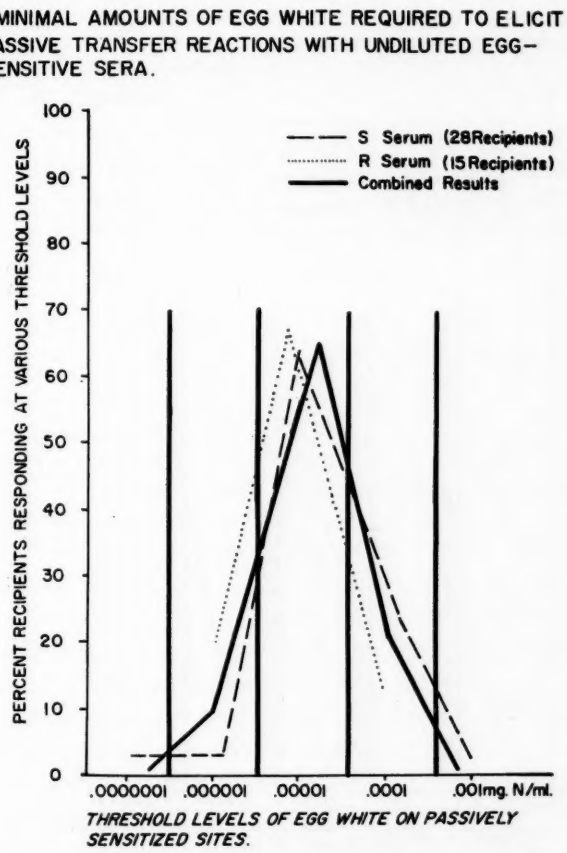

Fig. 1.

Serum R was studied in a similar manner in fifteen recipients. In ten of the fifteen subjects (66 per cent), the concentration of egg white solution required to elicit a threshold reaction was 0.00001 mg. N per milliliter (Fig. 1). Three recipients showed a threshold response at the level of 0.000001 mg. N per milliliter. In two recipients, the threshold response was elicited with egg white solution containing 0.0001 mg. N per milliliter.

As revealed in Fig. 1, the distribution curve of threshold responses to egg white with R serum is almost identical to that obtained with S serum. It seemed reasonable, therefore, to combine the results obtained with both sera. The results thus represent the findings obtained in forty-three recipients.

Tests were then done with serial tenfold dilutions of the five brands of influenza virus vaccines on sites sensitized with undiluted sera S and R. The results are portrayed in Fig. 2. Of forty-three recipients tested with dilutions of brand A, nineteen (44 per cent) revealed a threshold response with a 1:10,000 dilution, and 20 (46 per cent) reacted with a 1:1000 dilution. Of thirty-

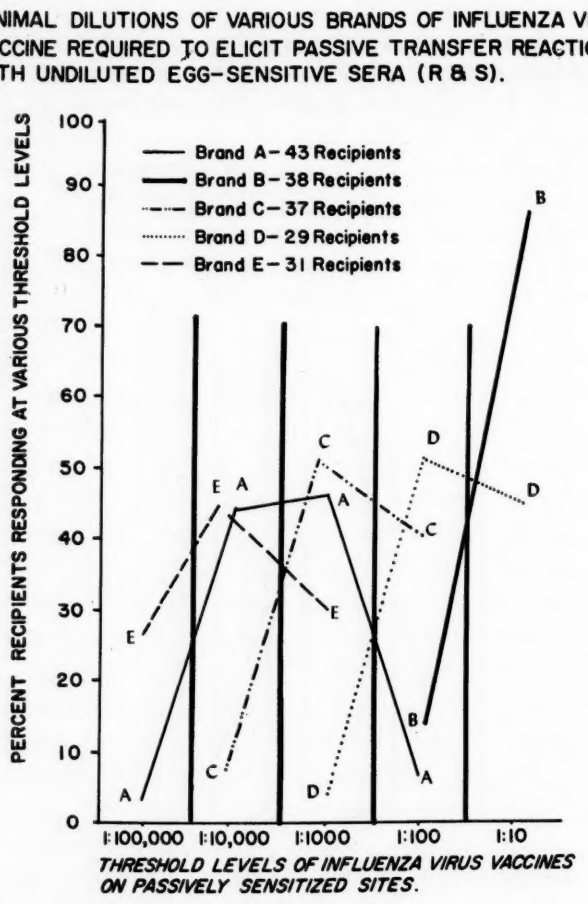

Fig. 2.

eight recipients tested with brand B, five (13 per cent) showed a threshold response to the 1:100 dilution and thirty-three (87 per cent) reacted to the 1:10 dilution. With brand C, the threshold response in nineteen of thirty-seven recipients (51 per cent) occurred with the 1:1000 dilution, and in fifteen recipients (40 per cent) with the 1:100 dilution. Among the twenty-nine recipients tested with brand D, the minimal dilution of vaccine which elicited

a passive transfer reaction was 1:100 in fifteen recipients (51 per cent) and 1:10 in thirteen recipients (45 per cent). With brand E, eight of thirty-one recipients (26 per cent) showed a threshold response at the level of 1:100,000 dilution, fourteen (45 per cent) responded minimally at the 1:10,000 level, and nine (29 per cent) responded at the 1:1000 level.

The responses of the majority of the recipients to the various brands of influenza virus vaccines formed several distinct patterns. Brands A and E, prepared by the chick red blood cell elution method, reacted mainly in the 1:10,000 to 1:1000 zone. Brands B and D, prepared by the Sharples centrifugation method, reacted predominantly in the 1:100 to 1:10 zone. Brand C, prepared by the protamine sulfate precipitation method, reacted in the 1:1000 to 1:100 zone.

By comparing the threshold reactions for egg white obtained in the majority of the recipients with those for the vaccines, it was estimated that the approximate content of egg white antigen in the vaccines is the following:

Brands B and D—0.0001–0.001 mg. N per ml.
Brand C —0.001 –0.01 mg. N per ml.
Brands A and E—0.01 –0.1 mg. N per ml.

DISCUSSION

Of the various antigenic components in vaccine of chick embryo origin, egg white has been shown to be the most active.[4] Thus, this antigen was used in these studies to indicate the approximate content of egg protein in various brands of influenza virus vaccine.

In previous reports on passive-transfer studies dealing with the content of egg protein in typhus vaccine, single passive-transfer tests were employed for each antigenic substance.[4] In view of the fact that recipients are known to vary in their responses to passive-transfer tests, it was considered necessary to employ numerous subjects in these semiquantitative studies.

The minimal concentration of egg white extract necessary to elicit a positive passive-transfer reaction on sites sensitized with two comparable reaginic sera was determined in forty-three nonsensitive subjects. In 65 per cent of these recipients, the threshold level for egg white was 0.00001 mg. N per milliliter.

The threshold passive-transfer response to influenza virus vaccine was then determined with dilutions of five brands of vaccine in numerous subjects. Although threshold reactions ranged from 1:10 to 1:100,000 dilutions of the various brands, definite patterns of response were evident, which seemed related to the method employed in concentrating the virus during preparation of the vaccine. Brands A and E, which were concentrated by the red blood cell elution method, responded predominantly to the 1:10,000 to 1:1000 dilutions. Brands B and D, which were concentrated by the Sharples centrifugation method, responded predominantly at dilutions of 1:100 to 1:10. Brand C, concentrated by the protamine sulfate precipitation method, responded mainly at the 1:1000 and 1:100 levels. By comparing the threshold responses obtained in the majority of recipients to egg white, the approximate amount of egg white antigen in

influenza virus vaccine was estimated. Those vaccines concentrated by the Sharples centrifugation method contained the least amount of egg white antigen, the approximate equivalent of 0.001 to 0.0001 mg. N per milliliter. Those vaccines concentrated by the red blood cell elution method contained the highest concentration of egg white antigen, the approximate equivalent of 0.01 to 0.1 mg. egg white antigen N per milliliter. Vaccines, concentrated by the protamine sulfate precipitation method, contained egg white antigen to the approximate equivalent of 0.001 to 0.01 mg. N per milliliter. Thus vaccines prepared by the red blood cell elution method contained approximately ten to one thousand times more egg white antigen than vaccines prepared by the other methods.

A recent report by Cohen and Mines[5] is of interest in relation to the studies herein described. These authors studied the egg white and egg yolk content of the same brands of influenza virus vaccine used by us. They employed the gel diffusion technique of Ouchterlony, with anti-egg white and anti-egg yolk rabbit serum. Differences in egg white antigen content in the various vaccines were demonstrated. In their studies however, no precipitin bands were found with those vaccines which were concentrated by Sharples centrifugation. On the basis of their results, one might gain the impression that this type of vaccine is devoid of egg white antigen. In the passive-transfer studies described herein, those brands of vaccines which were concentrated by Sharples centrifugation method were found to contain egg white antigen, although in lesser amounts than in the other brands. This finding demonstrates the greater sensitivity of the passive-transfer technique as compared to the gel diffusion method for this type of study.

As was previously mentioned, the Sharples centrifuged vaccines contained approximately 0.001 to 0.0001 mg. of egg white antigen N per milliliter. Thus, a prophylactic dose of this vaccine would contain about ten to one hundred times more antigen than is present in the average intracutaneous test with egg white. Although it is possible that patients with mild egg sensitivity might be able to tolerate such doses without untoward effects, it should be considered hazardous to use any of these egg-containing vaccines in an egg-sensitive individual. In view of the demonstrated fact that the influenza virus vaccines concentrated by the Sharples centrifugation method contain the least amount of egg white antigen, it would be wise to use this type of vaccine, especially in mass immunization programs when adequate allergic histories may not be obtained.

SUMMARY AND CONCLUSION

The present investigation was undertaken to determine the egg antigen content of various brands of influenza virus vaccine. Since egg white has been shown to be the most active antigen in vaccine of chick embryo origin, it was used as the indicator to estimate the amount of egg protein in the virus vaccines. Passive-transfer studies were done on forty-three normal recipients,

numerous trials being made with each dilution of egg white solution and five brands of vaccine. The approximate amount of egg white antigen in influenza virus vaccine was estimated by comparing the concentration of egg white extract needed to elicit a threshold passive-transfer reaction in the majority of recipients with the equivalent responding dilutions of the brands of vaccine.

The results indicate that influenza virus vaccines concentrated by the Sharples centrifugation method contained less egg white antigen, by a factor of ten to one thousand, than vaccines concentrated by chick red blood cell elution or the protamine sulfate precipitation methods. For this reason it is suggested that Sharples centrifuged vaccines be used for mass immunization programs. However, even those vaccines which have been found to contain the least amount of egg white antigen may not be safe to administer to egg-sensitive individuals.

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IMMUNE SERA IN THE STUDY OF FOOD ANTIGENS

III. Vegetable Seed Oils

Sheldon G. Cohen, M.D., Wilkes-Barre, Pa.*

AN EXACT etiological role for the edible vegetable oils as allergens in hypersensitivity states of man has not been clearly delineated. This was again emphasized to the Committee on Food Allergy of the Research Council of the American Academy of Allergy in recent attempts to evaluate the conflicting clinical evidence offered in the literature[1] and by divergent opinions submitted to us by qualified allergists. We have therefore undertaken to study this still unresolved question through animal experimentation and clinical investigation. This report is concerned with an initial phase of the project in which the specific precipitinogenic activity of immune rabbit sera has been employed in the detection of antigenic vegetable seed fractions. The value of this type of experimental approach has been previously demonstrated in related studies concerned with the detection of antigenic fish components in pharmaceutical fish liver oil preparations.[2]

MATERIALS AND METHODS

Immunizing dosages and schedules for the preparation of rabbit antisera, techniques for agar-gel plate double-diffusion precipitin tests (Ouchterlony) for qualitative antigenic analyses, and the preparation of aqueous phase extracts of water-in-oil dispersions were identical to those previously reported in the study of fish extracts and fish liver oils.[2] Briefly these consisted of the following: (1) preparation of standard saline extracts of cottonseed, corn, olive, peanut, and soybean; (2) immunization of series of rabbits, each with 12 mg. protein nitrogen of a vegetable extract; (3) determination of the number of individual precipitating antibody-antigen systems for each vegetable extract and its corresponding antiserum by agar-gel double-diffusion techniques; (4) preparation of water-in-oil dispersions of each edible vegetable oil (cottonseed, corn, peanut, soybean); and (5) separation of the aqueous phase (extract) of the water-in-oil and its subsequent employment in agar-gel double-diffusion tests with corresponding antiserum to the whole vegetable extract.

From the Department of Biology, Wilkes College.

This study was sponsored by the Committee on Food Allergy of the Research Council, American Academy of Allergy.

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*Associate professor of Biological Research.

Two lots each of seven different commercial brands of cottonseed oil, five of corn oil, three of peanut oil, and two of soybean oil were purchased on the open market. These were then studied for the possible presence of antigenic constituents that might show reactions of identity with the precipitin-producing fractions of the vegetable seed of its derivation.

RESULTS

The results of multiple agar-gel diffusion precipitin tests employing each antiserum to a vegetable seed extract with (a) its corresponding extract and (b) the aqueous phase of the corresponding water-in-vegetable oil preparation are summarized in Table I.

TABLE I

EXTRACT OF:	ANTISERUM TO:	NUMBER OF PRECIPITIN BANDS
Cottonseed	Cottonseed	8*
Cottonseed oil		
Brand A	Cottonseed	3*
Brand B	Cottonseed	2*
Brands C-G	Cottonseed	0
Corn	Corn	2*
Corn oil		
Brand A	Corn	1*
Brands B-E	Corn	0
Peanut	Peanut	4
Peanut oil		
Brands A-C	Peanut	0
Soybean	Soybean	12
Soybean oil		
Brands A-B	Soybean	0

*Reactions of identity were demonstrated between precipitin bands developed in the same agar plate containing each extract diffusing against a common antiserum.

COMMENT

The multiplicity of distinct antigenic components within cottonseed, corn, peanut, and soybean is demonstrated by their serum precipitin-producing properties in rabbits. The presence of some of these same water-soluble antigens within some lots of derivative oils of cottonseed and corn, but not peanut or soybean, is also demonstrated by immunologic techniques of identification. An attempt to evaluate olive oil by similar study was not possible since we were unable to prepare an olive extract of sufficient antigenicity to induce the formation of precipitating serum antibody in the rabbit by the technique employed.

It is of special interest to take note of a study[3] reporting quite similar differences in these oils by analytic chemical techniques. Peanut oil was found relatively free of non-oil constituents in contrast to other edible seed oils, especially cottonseed and corn, showing such contents of 2 per cent or more. While crude soybean oil was also found to contain large amounts of nonglycerid material, this was effectively reduced by premarketing treatment.

Proteins and protein fragments are known to be soluble in oil when in anhydrous form. It is therefore understandable that the extent of removal of

native seed proteinaceous substances is only proportional to the efficacy of "degumming" processes such as solvent extraction, steam, or weak alkali treatment of the vegetable oil.[4] The variable presence of some seed antigenic contaminants in derivative oils thus becomes a distinct possibility. In further consideration of untoward reactions to cottonseed, Friedman[5] has been studying the clinical importance of its gossypol content, a water-insoluble fraction with irritating properties to the gastrointestinal tract.[6]

It is to be pointed out that the identity of antigens of cottonseed and corn responsible for precipitin formation in the rabbit and allergens of similar origin for man have not been established. However, the possibility of relationship merits consideration in speculating on clinical applications of these findings. Interest is directed to the inconstant presence and the variability in number of individual water-soluble vegetable seed antigens within different lots of the final derivative oil product. Thus, along with a quantitative factor, perhaps another important determinant of allergic reactivity for any edible vegetable seed oil may be the variable presence or absence of that particular antigenic seed fraction for which the individual possesses reagins and/or clinical sensitivity. Qualitative and quantitative antigenic analyses of each lot of cottonseed oil employed may be prerequisite to evaluating clinical observations that only the infrequent cottonseed-sensitive patient is intolerant to cottonseed oil and that even the same individual may not react in a constant symptomatic pattern to each trial ingestion.

SUMMARY

1. Sera from specifically immunized rabbits were employed in agar-gel double-diffusion precipitin test techniques for the qualitative antigenic analyses of cottonseed, corn, peanut, and soybean extracts and their edible derivative oils.

2. Eight antigenic components were demonstrated in cottonseed extracts, two in corn, four in peanut, and twelve in soybean.

3. Two to three of these water-soluble seed antigens were demonstrated in two out of seven brands of commercial cottonseed oil and one antigenic fraction in one of five brands of corn oil by immunologic techniques of detection.

4. Water-soluble antigens of peanut and soybean could not be detected in the lots of their derivative oil preparations tested.

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AMERICAN ACADEMY OF ALLERGY

REPORT OF THE RESEARCH COUNCIL COMMITTEE FOR 1959

THIS REPORT is divided into two sections: (1) reports of the individual committees, and (2) a report on general and administrative matters pertaining to the Research Council Committee as a whole.

I. COMMITTEE REPORTS

1. *Committee on Pollen and Molds.*—Together with many collaborators, this committee continues to compile the results of pollen and mold counts in numerous areas of the United States and Canada. Seven members are promoting, directing, or consulting with regional studies, the most ambitious of these being the operation of 22 sampling stations in the San Francisco Bay area under the auspices of the Allergy Foundation of Northern California. The aeroallergen survey of the Virgin Islands National Park has been completed with the finding of no ragweeds or ragweed pollen and minimal quantities of grass pollen. Two committee members are running parallel gravimetric-volumetric counts using Marx impingers, and one committee member is sponsoring several pollen counting projects in high schools. The committee has been following, with interest, basic projects in pollen research at the Brookhaven National Institute, at the University of Michigan, and at Kansas State College. In November the chairman presented at the Dallas Health Fair the hay fever exhibit which has been used for the past several years at the Chicago Museum of Science and Industry. He also continues to answer a large number of inquiries from physicians and laymen.

The Herbarium sent a total of 629 pollen specimens in response to 28 requests for such materials. This represents an increase of about two and one-half times over requests received in 1958.

To avoid possible unfair favoring of one resort area over another, the committee hereafter will present pollen index data on a regional basis only.

Membership: Oren C. Durham, Chairman for Pollen; Dr. David Merksamer, Chairman for Molds; Dr. Ralph Voigt, Curator of the Herbarium; Drs. Samuel C. Bukantz, Ben L. Eisenberg, Bernard T. Fein, Lowell Henderson, Eloise W. Kailin, W. W. G. Machlachlan, Lawrence Maslansky, Dean A. Moffat, Eugene C. Ogden, Frank Perlman, Merle S. Scherr, Bernard B. Siegel, Jay Spiegelman, A. M. Targow, and Matthew Walzer.

2. *The Committee on Insects.*—This group has continued activities of previous years, including the preparation of insect extracts and their distribution to

collaborating physicians, supplying information about insect allergy to individuals and to medical publications, and identification of insects sent in to the committee (chiefly of the biting and stinging variety). The consulting entomologist has participated in collecting and identifying insect materials for the committee.

Membership: Dr. Frank Perlman, Chairman; Drs. James H. Barnard, Harry S. Bernton, I. Leonard Bernstein, Norman K. Cohen, Rubin Grossman, I. M. Hinnant, Sidney W. Jennes, Merle S. Scherr, and Joel D. Teigland.

3. *The Committee on Weather.*—This committee again conducted a study attempting to correlate meteorological factors with incidences of asthma in a number of cities in the United States during November, 1959. Results of a similar study carried out during 1958 have been tabulated.

Membership: Dr. Harold S. Tuft, Chairman; Drs. John F. Beakey, I. Leonard Bernstein, Armand Cohen, Norman K. Cohen, Seymour B. Crepea, Frank F. Furstenberg, Dan Goodman, Lowell Henderson, Macy I. Levine, James A. McLean, Frank Perlman, Merle S. Scherr, Paul M. Seebohm, and Paul VanArsdel, Jr.

4. *Committee on Air Processing.*—This committee continues to answer inquiries about air filtration devices. Based on its many years' experience in testing this type of apparatus, it is preparing another report to the Academy on recommended specifications for acceptable air filtration units.

Membership: Dr. Willard S. Small, Chairman; Dr. Susan C. Dees.

5. *The Committee on Contactants.*—This group has continued its functions of collecting information regarding recently recognized contactants and acting as an advisor to governmental agencies, especially the FDA. In regard to the latter, opinions were submitted concerning reactions to deodorants. Many of these are due to the aluminum salts, whereas zirconium granulomas constitute another group. The FDA itself has compiled data on the sensitizing capacities of various substances with which humans are in contact.

Membership: Dr. Max Grolnick, Chairman; Drs. Rudolf L. Baer, Donald J. Birmingham, George H. Curtis, Merrill W. Chase, Naomi M. Kanof, John L. Fromer, Irvin Kerlan, Morris Leider, Rudolf Mayer, Samuel M. Peck, Marion B. Sulzberger, and Raymond R. Suskind.

6. *The Committee on Drugs.*—This group has been engaged in evaluating three drugs, two of these being new antihistamines. The possibility of evaluating several additional new drugs is under consideration. Some changes in the method of collecting data on new drugs are planned for the future.

In addition, representatives of the committee met with representatives of the American College of Radiology regarding collaboration in a joint group study on reactions to injectable agents. This study was initiated primarily by the radiologists, but Academy collaboration was requested particularly in a consultant capacity regarding the possible role of allergy in these reactions.

Membership: Dr. Sidney Friedlaender, Chairman; Drs. Murray M. Albert, Robert J. Becker, Theodore B. Bernstein, Earl B. Brown, Monroe Coleman, Seymour Crepea, Edmund E. Ehrlich, J. D. L. Fitzgerald, Alex S. Friedlaender, Henry T. Friedman, Harold J. Friedman, Joseph B. Fries, Claude A. Frazier, Frank T. Joyce, Louis Levin, Samuel J. Levin, Lloyd Mayer, Dean A. Moffat, Milton Mosko, George A. Peck, Gustavus Peters, Isadore Pitesky, Norman B. Richard, Simon Rubin, Irving W. Schiller, Bert B. Schoenkerman, Paul M. Seebohm, Sheppard Siegel, Aaron D. Spielman, Samuel J. Taub, Paul VanArsdel, Jr., and William G. Woodin.

7. *Reaginic Serum Bank.*—At the direction of the Academy Executive Committee, the Reaginic Serum Bank has ceased sending out sera because of possible medicolegal risks. Consideration is being given to replacing it with an active registry of reaginic sera or reaginic serum donors.

Membership: Dr. Bernard B. Siegel, Chairman.

8. *Committee on Food Allergy.*—Some of the major projects of the Committee on Food Allergy for the year were dependent upon sera supplied by the Reaginic Serum Bank, and these have been abandoned.

The Committee Chairman has continued with a series of studies on reactions of immune sera with food antigens. Under committee sponsorship, papers dealing with fish and with crustacean antigens have been published within the last year in the JOURNAL OF ALLERGY, and an additional study concerning possible contamination of commercial and edible vegetable oils with their natural protein antigens is nearing completion. Other work in progress relates to possible cross antigenicity of tree pollens and fruit. Another committee member has shown by passive-transfer tests the presence of partial cross antigenicity among fish extracts, regardless of classification and edibility.

The FDA has sought the assistance of the committee in obtaining names of persons qualified to express an authoritative opinion regarding the possible allergenicity of various food additives, and liaison with the committee is being maintained. The committee hopes also to keep the Academy membership and medical profession at large informed as to new information regarding allergenic foods and potentially sensitizing ingredients of commercial food products.

Membership: Dr. Sheldon Cohen, Chairman; Drs. James H. Barnard, Katherine Bowman, Mario Fabi, George Frauenberger, Stanley S. Freedman, Henry T. Friedman, Joseph H. Fries, Eloise W. Kailin, Morris Kaplan, Macy I. Levine, Saul Malkiel, Lloyd Mayer, Albert H. Rowe, Bernard B. Siegel, Margaret Strauss, Abram Targow, and Richard Wiseman.

Advisory Board to the Research Council Committee: Drs. Samuel M. Feinberg, Harry Hayes, Alfred Gilman, Irvin Kerlan, William Sherman, Matthew Walzer, and Charles Woodworth.

II. ADMINISTRATIVE REPORT

There were 120 appointments to the Research Council Committees in 1959 as compared to 119 in 1958. A new set of rules governing the Research Council

Committee was adopted at the annual meeting of the committee on Jan. 9, 1960. This incorporates the old Research Council constitution, its 1958 amendments, and the changes in the Academy by-laws pertaining to this group voted upon in 1959. Other actions taken by the Research Council Committee included the establishment of a Reaginic Serum Registry and the establishment, at the suggestion of the Executive Committee, of a committee concerned with specific injection therapy for allergy. Dr. Seymour Crepea was appointed to succeed Dr. Sidney Friedlaender as Chairman of the Committee on Drugs. A policy was adopted of exhibiting at the annual meeting committee reports containing specific factual information of interest to the Academy membership.

In completing my three-year term as Chairman of the Research Council Committee, I would like to comment upon the over-all direction of this committee's work in recent years and prospects for the future. A major effort has been made to set realistic goals for a voluntary organization of this type, to establish an equitable and democratic procedure for determining membership, to simplify organization, and to assure an active program of group research. This latter goal has been only partially realized. It would be a mistake, however, to judge the Research Council Committee on the basis of its group research productivity alone. On numbers of occasions, component committees have served capably in an advisory capacity to various federal agencies. Some sections have taken on the significant task of serving as a registry for the collection and dissemination of recent technical information in their respective fields. The educational aspects of membership on these committees also are not to be overlooked. Committee members have a real opportunity to participate *actively* in small committee discussions. Possibly such opportunities and the sense of belonging to a group with similar special interests may serve to nurture a spark of enthusiasm which can make the practice of allergy more stimulating and satisfying. Finally, it may be profitable for the Research Council Committee to be more active in regard to its avowed objective of stimulating research in allergy. With very limited numbers of well-qualified persons entering research careers in the biological sciences, allergy cannot afford to ignore the stiff competition it faces from a host of other clinical disciplines for the attention and interest of this scarce talent. A major problem for the future will be to integrate these objectives of the Research Council Committee with an active program of group investigation.

Respectfully submitted,
Kenneth P. Mathews, M.D.
Chairman

ANNOUNCEMENTS

Two Allergy Residencies Available in Pittsburgh

Two approved one-year residencies are available, one at the U. S. Veterans Hospital and the other at the Montefiore Hospital, Pittsburgh, Pennsylvania. Address inquiries to Leo H. Criep, M.D., The Bigelow, Pittsburgh 19, Pennsylvania.

Postgraduate Course in Allergy in Philadelphia

A continuous course of two weeks' duration is being offered by the Departments of Allergy and Applied Immunology of the Temple University Medical Center and the Graduate School of Medicine of the University of Pennsylvania. Sessions will be held daily at the Temple University Medical Center, from 9:00 A.M. to 5:00 P.M. from February 27 to March 10, 1961. The tuition is $175.00 and the enrollment is limited. Dr. Louis Tuft is course director, with Drs. George Blumstein and Merle M. Miller as associate directors.

An outstanding faculty has been assembled to review the basic principles of immunology and allergy as applied to clinical practice. Emphasis will be given to the methods of diagnosis and management of the allergic patient.

The course is designed for physicians desirous of extending their knowledge of allergy. It could serve as an introductory course for those about to enter the field or as a review course for practicing allergists.

For brochure and application forms write to Dr. George Blumstein, c/o Temple Medical Center, Philadelphia 40, Pennsylvania.

Allergy Sessions in Argentina

A series of Allergy Conferences will be held in Rosario, Argentina, on Nov. 28, 29, 30, 1960, under the auspices of the Post-Graduate Medical School, National University of the Litoral.

A second series of meetings will be held on Dec. 1, 2, 3, 1960, under the auspices of the Departments of Hygiene and of Social Medicine of the School of Medicine, Buenos Aires National University, in Buenos Aires.

Members of the Academy are cordially invited to attend these meetings covering the field of allergy and associated fields. A member who has a worth-while contribution to present at one of these meetings is requested to correspond with Dr. Leon Bentolila, Jefe Del Centro De Alergia, San Lorenzo 1150, Rosario, Argentina.

A special flight has been arranged by the Argentine Airlines on Jet "Comet 4," round trip between New York and Buenos Aires. The cost of this will be $450.00, including tax. Discount will be allowed on hotel bills and transportation inside Argentina.

Course Sponsored by American Thoracic Society

The eleventh annual presentation of a course on "The Measurement of Pulmonary Function in Health and Disease" will take place at the Boston City Hospital from March 27 to March 31, 1961. The course will be sponsored as in the past by the American Thoracic Society and the three medical schools of Boston. Tuition is $100.00 ($75.00 for members of the American Thoracic Society). Applications should be directed to: Edward J. Welch, M.D., 1101 Beacon Street, Brookline, Massachusetts.

BOOKS RECEIVED

Atlas and Manual of Dermatology and Venereology. By Professor Dr. W. Burckhardt. Translated and edited by Stephan Epstein, M.D. Baltimore, 1959, Williams & Wilkins Company. 276 pages. Price $14.00.

Chemical Quantitation of Epinephrine and Norepinephrine in Plasma. By William Muir Manger, B.S., M.D., Ph.D., Khalil G. Wakim, M.D., Ph.D., and Jesse L. Bollman, M.D. Springfield, Ill., 1959, Charles C Thomas. 398 pages. Price, $11.50.

Atopic Cataract. By Emanuel Rosen, M.D. Springfield, Ill., 1959, Charles C Thomas. 102 pages.

Ciba Foundation Colloquia on Ageing—The Lifespan of Animals. Vol. 5. G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Maeve O'Connor, B.A. (editors). Boston, 1959, Little, Brown & Company. 324 pages. Price, $9.50.

Ciba Foundation Symposium—Cellular Aspects of Immunity. G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc. (editors). Boston, 1959, Little, Brown & Company. 495 pages. Price, $10.50.

Xylocaine—The Pharmacological Basis of Its Clinical Use. By Sten Wiedling. Stockholm, 1959, Almquist and Wiksell. 146 pages.

Allergia—Malattie Allergiche Ed Allergosimili. Vol. I—700 pages. Vol. II—2214 pages. By Guido Melli. Milan, Italy, 1959, Casa Editrice, Dr. Francesco Vallardi.

Lymphocytes and Mast Cells. By Margaret A. Kelsall, B.A., M.A., Ph.D., and Edward D. Crabb, B.A., M.A., Ph.D. Baltimore, 1959, Williams & Wilkins Company. 399 pages. Price, $8.00.

Alergia Clinica. Principales Caracteristicas en Mexico. Vol. I. Vol. II—1040 pages. By Dr. Jose Luis Cortes. Mexico, 1958, Impresiones Modernas, S.A.

Steroids. By Louis F. Fieser and Mary Fieser. New York, 1959, Reinhold Publishing Corporation. 945 pages. Price, $18.00.

Dermatologie und Venerologie. Vols. I and II—1401 pages. By Prof. Dr. H. A. Gottron and Prof. Dr. W. Schonfeld. Stuttgart, Germany, 1959, Georg Thieme Verlag, and New York, 1959, Intercontinental Medical Book Corporation.

Current Problems in Allergy and Immunology. William Kaufman (editor). Basel/New York, 1959, S. Karger. 992 pages. Price, sFr 60.

Studies on the Technique of Skin Testing in Allergy. By W. J. F. Van Der Bijl, M.D. Springfield, Ill., 1960, Charles C Thomas, and Leiden, Holland, 1960, H. E. Stenfert Kroese N. V. 100 pages. Price, $5.50.

Ciba Foundation Study Group No. 4—Virus Virulence and Pathogenicity. G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Cecilia M. O'Connor, B.Sc. (editors). Boston, 1960, Little, Brown & Company. 114 pages.

The Office Assistant in Medical Practice. Second edition. By Portia M. Frederick and Carol Towner. Philadephia/London, 1960, W. B. Saunders Company. 407 pages. Price, $5.25.

Fundamentals of Modern Allergy. Samuel J. Prigal, M.D. (editor). New York/Toronto/London, 1960, McGraw-Hill Book Company, Inc. 690 pages. Price, $18.50.

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